

Chapter 2

Total Synthesis through Palladium-Catalyzed Bis-Cyclization of Bromoallenes

Abstract Palladium(0)-catalyzed cyclization of bromoallenes bearing hydroxy and benzamide groups as internal nucleophiles stereoselectively provides functionalized tetrahydrofuran. This cyclization was expanded to divergent synthesis of pachastrissamine, a biologically active marine natural product, and its derivatives.

Pachastrissamine **1** (Fig. 2.1), an anhydrophytosphingosine derivative isolated from a marine sponge *Pachastrissa* sp., was reported by Higa et al. in 2002 [1]. Shortly thereafter, Debitus et al. isolated the same compound from a different marine sponge, *Jaspis* sp., and named jaspine B [2]. Other structurally related analogues have also been isolated from the same species, including jaspine A and 2-*epi*-jaspine B. Pachastrissamine (jaspine B) **1** exhibits cytotoxic activity against various tumor cell lines at nanomolar level [1, 2]. In 2009, Delgado et al. reported that dihydroceramides mediated autophagy might be involved in the cytotoxicity [3]. Andrieu-Abadie et al. indicated that pachastrissamine induces apoptotic cell death in melanoma cells by a caspase-dependent pathway [4]. Owing to its biological importance, pachastrissamine has been the target of many synthetic studies (for previous syntheses [5–23]). Stereoselective construction of the tetrahydrofuran ring which bears three contiguous stereogenic centers is a major issue in the total synthesis.

As described in Chap. 1, the author planned domino cyclization of type **2** bromoallenes or type **3** propargyl compounds bearing nucleophilic groups at the both ends of a branched alkyl group, which would directly lead to bicyclic products such as **6** or **7** (Scheme 2.1). 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 **4** or **5**, respectively. These would be converted to the cyclic products **6** or **7**, respectively, by the second intramolecular reaction.

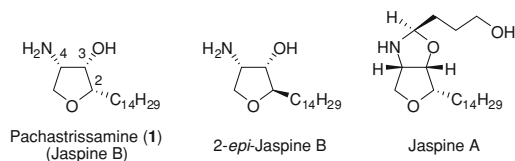
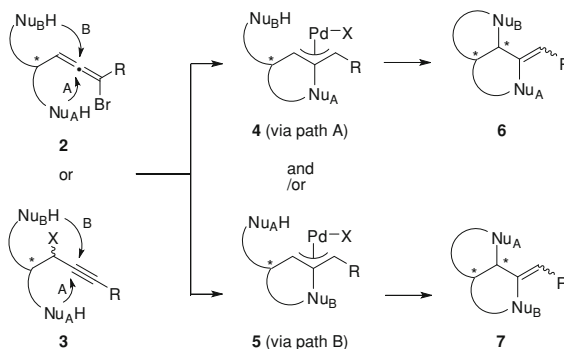


Fig. 2.1 Structures of naturally occurring jaspines

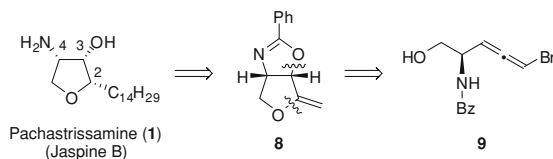


Scheme 2.1 Construction of bicyclic structures by palladium(0)-catalyzed cascade cyclization of bromoallenes **2** and propargyl compounds **3**

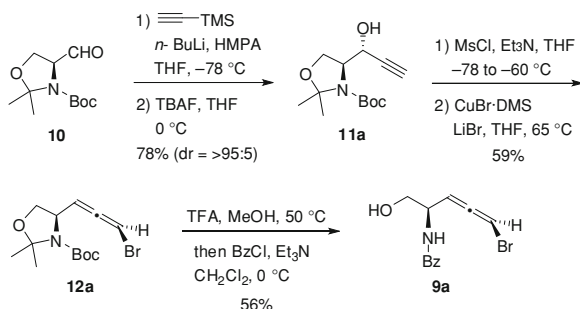
The author is also interested in the stereochemical course of the domino cyclization, *i.e.* the effect of the axial or central chirality in the allenic/propargylic moiety of **2/3** on the reactivity and selectivity. The author chose pachastrissamine **1** for the model study to evaluate this working hypothesis on the ring-construction/stereoselective functionalization cascade.

The author expected that palladium(0)-catalyzed cyclization of bromoallenes **9** bearing hydroxy and benzamide groups [24–26] as internal nucleophiles could regio- and stereoselectively provide appropriately functionalized tetrahydrofuran **8** for synthesis of pachastrissamine **1** (Scheme 2.2). The bicyclic structure of **8** including the exo-olefin would be useful for stereoselective construction of a C-2 stereogenic center as well as carbon homologation. This synthetic route takes an advantage of the late-stage introduction of the long alkyl side chain into the tetrahydrofuran ring at the C-2 position, which makes it possible to achieve a divergent synthesis of pachastrissamine derivatives.

Preparation of the required bromoallene **9a** is outlined in Scheme 2.3. The *erythro*-alkynol **11a** was easily prepared from (*S*)-Garner's aldehyde **10** [27, 28] following the literature procedure [29]. Treatment of **11a** with MsCl and Et₃N gave the corresponding mesylate, which was then allowed to react with CuBr·DMS/LiBr [30, 31] (DMS = Me₂S) to afford the (*S,aR*)-bromoallene **12a**.



Scheme 2.2 Retrosynthetic analysis of pachastrissamine **1**

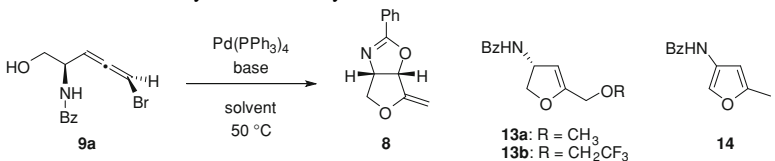


Scheme 2.3 Synthesis of bromoallene **9a**

(preparation of **12** was previously reported in Refs. [32, 33]).¹ Removal of the Boc and acetal groups with TFA followed by acylation with BzCl/Et₃N afforded the benzamide **9a**.

The author next investigated cascade cyclization of bromoallene **9a** in the presence of palladium(0) (Table 2.1). Treatment of **9a** with Pd(PPh₃)₄ (5 mol %) and NaH (2.0 equiv) in MeOH at 50°C (standard conditions for cyclization of bromoallenes) [34, 35] successfully produced the desired bicyclic tetrahydrofuran **8** in 50% yield (entry 1). The undesired cyclization initiated by the first cyclization by the benzamide group (Scheme 2.1) was not promoted. However, the anticipated side-products dihydrofuran **13a** (formed by the intermolecular reaction with methoxide) and a small amount of furan **14** were observed. Formation of the furan **14** can be rationalized by β -hydride elimination of the η^3 -allylpalladium intermediate (e.g. **4** or **5**, Scheme 2.1) followed by aromatization. (a related furan formation as a by-product in the cascade cyclization of propargylic bromides was recently reported, see Ref. [36]). 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 **8** and **13a** (40 and 15%, respectively), while the amount of furan **14** increased (10% yield, entry 2). Of the several bases investigated, Cs₂CO₃ (1.2 equiv) most effectively produced the desired product **8** and suppressed formation of furan **14** (entries 2–5). The best result was obtained using a mixed solvent of THF/MeOH

¹ For improvement of the yield of **12**, a slightly modified bromination protocol was used (3 equiv of the copper reagent, 65°C ; see the Experimental Section).

Table 2.1 Palladium-catalyzed cascade cyclization of bromoallene **9a**^a


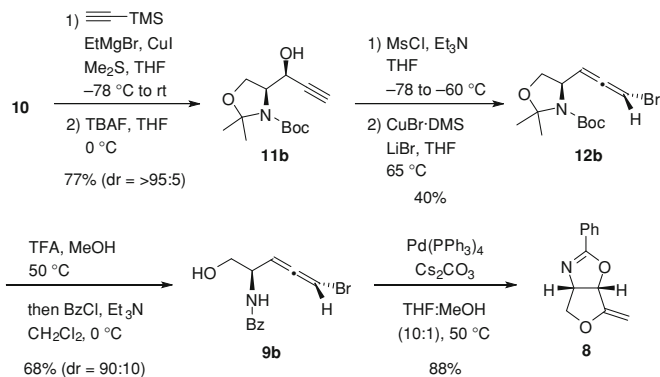
Entry	Base (equiv)	Solvent	Yield (%) ^b			Recovery (%) ^c
			8	13	14	
1	NaH (2.0)	MeOH	50	45	trace	–
2	NaH (2.0)	THF/MeOH (4:1)	40	15	10	–
3	K ₂ CO ₃ (2.0)	THF/MeOH (4:1)	43	–	–	41
4	Cs ₂ CO ₃ (2.0)	THF/MeOH (4:1)	67	26	–	–
5	Cs ₂ CO ₃ (1.2)	THF/MeOH (4:1)	78	20	–	–
6	Cs ₂ CO ₃ (1.2)	THF/MeOH (10:1)	89	trace	–	–
7	Cs ₂ CO ₃ (1.2)	THF	12	–	–	64
8	Cs ₂ CO ₃ (2.0)	THF/TFE (4:1)	–	93	–	–
9	Cs ₂ CO ₃ (2.0)	THF/ <i>t</i> -BuOH (4:1)	12	–	–	60

^a All reactions were performed with 5 mol % Pd(PPh₃)₄ at 0.1 M for 1–4 h^b Yield of isolated products^c Recovery of starting material. TFE = 2,2,2-trifluoroethanol

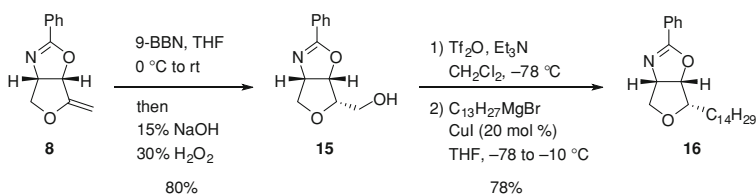
(10:1) in the presence of 1.2 equiv of Cs₂CO₃ (89%, entry 6). It should be noted that the use of solely THF resulted in low yield of **8** (12%, entry 7) and recovery of the starting material, which suggests that an alcoholic solvent plays an important role in this type of transformation. Interestingly, use of CF₃CH₂OH, a more acidic solvent which might facilitate the protonation step, only gave the undesired compound **13b** bearing a trifluoroethoxy group in high yield (93%, entry 8). Moreover, use of *t*-BuOH was not effective (entry 9). These results indicate that p*K*_a values and bulkiness of the alcoholic solvents have significant effects on the reaction, i.e. the intramolecular vs. intermolecular reaction in the second nucleophilic attack, and reactivity of the bromoallene with a palladium catalyst.

To investigate the difference in reactivity between the diastereomeric bromoallenes **9a** and **9b**, the author next synthesized (*S,aS*)-bromoallene **9b**, also starting from Garner's aldehyde **10** (Scheme 2.4). The *threo*-alkynol **11b**, stereoselectively obtained following Taddei's protocol (preparation of **12** was previously reported in Ref. [32, 33])², was converted into the desired bromoallene **9b** in the same manner as described above (Scheme 2.3). Bromoallene **9b** was then subjected to the optimized reaction conditions shown in entry 6 (Table 2.1) to give the desired bicyclic product **8** in 88% yield. These results show both bromoallenes **9a** and **9b** equally undergo the cascade cyclization to give the same product **8**. This means that a diastereomeric mixture of bromoallenes can be directly employed for preparation of **8**.

² For improvement of the yield of **12**, a slightly modified bromination protocol was used (3 equiv of the copper reagent, 65 °C; see the Experimental Section).



Scheme 2.4 Synthesis and palladium-catalyzed cascade cyclization of the epimeric bromoallene **9b**

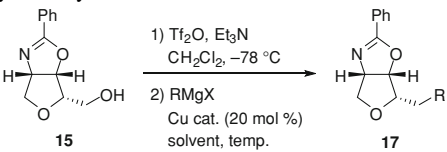


Scheme 2.5 Synthesis of protected pachastrissamine (**16**)

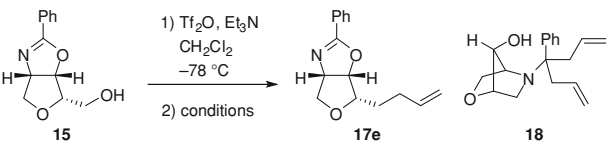
With the functionalized tetrahydrofuran **8** prepared, the author examined the introduction of a C-2 alkyl side chain with an all-*cis* configuration. Hydroboration-oxidation of the exo-olefin of **8** with 9-BBN provided the primary alcohol **15** with the desired configuration as the sole diastereomer [37]. Treatment of **15** with TiF_2O and Et_3N followed by displacement with a cuprate derived from $\text{C}_{13}\text{H}_{27}\text{MgBr/CuI}$ provided the tetrahydrofuran **16** bearing all the requisite functionalities (Scheme 2.5) [38]. The cleavage of oxazoline ring will be described in Chap. 3.

The author next investigated the incorporation of diverse side chains into the C-2 position using a variety of organocopper reagents derived from Grignard reagents (Table 2.2). Reaction with Grignard reagents containing a primary alkyl group such as phenylethyl and methyl in the presence of a copper salt (20 mol %) afforded the desired alkylation products in good yields (entries 1, 2) [39, 40]. Changing the Grignard reagents to *i*-PrMgCl or $\text{CH}_2=\text{C}(\text{CH}_3)\text{MgBr}$ gave moderate yields of the corresponding products **17c** or **17d** (entries 3, 4), respectively, containing a secondary alkyl or alkenyl group [41]. The author next examined introduction of an allyl group, which can be readily used for further manipulation (Table 2.3). However, treatment of the triflate with allylMgBr and catalytic CuBr [39, 40] provided the unanticipated product oxazabicycloheptane **18** in 90% yield (entry 1). (Structure of **18** was confirmed by NMR analysis and comparison with structurally related compounds, see Ref. [42]). The reaction in the absence of a copper catalyst, also afforded **18** in 91% yield (entry 2). In comparison, use of

Table 2.2 Copper-catalyzed alkylation of triflates^a

					
Entry	RMgX	CuX cat.	Solvent	Temp.	Products (% yield) ^b
1	Ph(CH ₂) ₂ MgCl	CuI	THF	−78 °C to rt	17a (76)
2	MeMgBr	CuBr	THF:Et ₂ O (9:1)	−30 °C to rt	17b (82)
3	<i>i</i> -PrMgCl	CuBr·Me ₂ S	THF:Me ₂ S (30:1)	−20 to 0 °C	17c (54)
4	CH ₂ =C(CH ₃)MgBr	CuBr·Me ₂ S	THF:Me ₂ S (30:1)	−20 to 0 °C	17d (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 2.3** Copper-catalyzed allylation of triflates and formation of 2-oxa-5-azabicyclo[2.2.1]heptanes

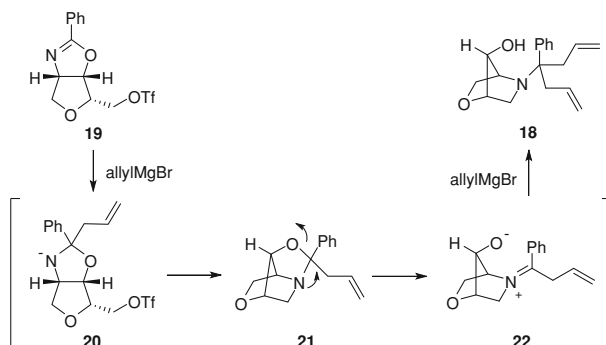
			
Entry	Conditions	Yield (%) ^{a,b}	
		17e	18
1 ^c	AllylMgBr, CuBr (20 mol%), THF:Et ₂ O (3:1), −30 °C	ND	90
2 ^c	AllylMgBr, THF:Et ₂ O (3:1), −30 °C	ND	91
3 ^d	(Allyl) ₂ Cu(CN)Li ₂ , THF, −78 °C	32	ca. 5

^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)Li₂ (4.0 equiv) for 30 min

(allyl)₂Cu(CN)Li₂ [43, 44] resulted in 32% yield of the desired product **17e** along with a small amount of the side product **18** (entry 3).

Rationale for formation of the oxazabicycloheptane **18** is depicted in Scheme 2.6. The addition of allylMgBr to imine followed by intramolecular attack of the resulting nitrogen anion to triflate would generate mono-allylated intermediate **21**. The second nucleophilic attack of allylMgBr to iminium cation **22** derived from **21** would proceed to give the oxazabicycloheptane **18**.³ Servi et al. also reported that 2-phenyloxazolines bearing a tosylate leaving group with allyl Grignard reagent gave bicyclic compounds similar to the intermediate **21** [45]. In contrast, the reaction with the other Grignard reagents did not afford the

³ Reaction of triflate **19** with 1.0 equiv of the allyl Grignard reagents gave the oxazabicycloheptane **18** in 13% yield along with the recovery of the unchanged triflate **19** in 73% yield, without isolation of the intermediate **21**. This is presumably due to a highly strained aminor structure of **21** and facile Grignard reaction to the iminium moiety of **22**.



Scheme 2.6 Formation of 2-oxa-5-azabicyclo[2.2.1]heptane **18**

oxaazabicycloheptane-type products (Table 2.2). The formation of the oxaazabicycloheptane **18** with allylMgBr would be caused by the first addition to imine **19** proceeding through six-membered transition state.

In conclusion, the author has 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 protected pachastrissamine **16** and its derivatives **17** bearing three contiguous stereogenic centers from Garner's aldehyde as the sole chiral source.

2.1 Experimental Section

2.1.1 General Methods

All moisture-sensitive reaction were performed using syringe-septum cap techniques under an argon atmosphere and all glassware was dried in an oven at 80 °C for 2 h prior to use. Reactions at −78 °C employed a CO₂–MeOH bath. Melting points were measured by a hot stage melting point apparatus (uncorrected). Optical rotations were measured with a JASCO P-1020 polarimeter. For flash chromatography, Wakosil C-300, Wakogel C-300E or Chromatorex[®] was employed. ¹H NMR spectra were recorded using a JEOR AL-400 or JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS (in CDCl₃) as internal standard. ¹³C NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual CHCl₃ signal. ¹⁹F NMR spectra were recorded using a JEOL ECA-500 and referenced to the internal CFCl₃ (δ_F 0.00 ppm). ¹H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A

mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

2.1.2 *tert*-Butyl (*R*)-4-[(*R*)-3-Bromopropa-1,2-dienyl]-2,2-dimethyloxazolidine-3-carboxylate (**12a**)

To a stirred mixture of the propargylic alcohol **11a** [29] (5.66 g, 22.2 mmol) and Et₃N (15.4 mL, 111 mmol) in THF (70 mL) was added MsCl (3.40 mL, 44.4 mmol) at -78°C , and the mixture was stirred for 0.5 h with warming to -60°C . The mixture was made acidic with saturated NH₄Cl at -60°C , and the mixture was concentrated under reduced pressure. The residue was extracted with Et₂O. The extract was washed with H₂O and brine and was dried over Na₂SO₄. Concentration of the filtrate under reduced pressure followed by rapid filtration through a short pad of silica gel with Et₂O to give a crude mesylate, which was used without further purification. A mixture of CuBr·DMS (13.7 g, 66.6 mmol) and LiBr (5.80 g, 66.6 mmol) was dissolved in THF (70 mL) at room temperature under argon. After stirring for 2 min, a solution of the above crude mesylate in THF (90 mL) was added to this reagent at room temperature. The mixture was stirred at 65°C for 4 h and quenched with saturated NH₄Cl and 28% NH₄OH. The whole was extracted with Et₂O and the extract was washed with H₂O and brine and was dried over Na₂SO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (13:1) to give **12a** as a colorless oil (4.15 g, 59% yield). All spectral data were in agreement with those reported by Taddei [33].

2.1.3 *N*-[(2*R*,4*R*)-5-Bromo-1-hydroxypenta-3,4-dien-2-yl]benzamide (**9a**)

To a stirred solution of **12a** (200 mg, 0.629 mmol) in MeOH (0.30 mL) at 0°C was added trifluoroacetic acid (1 mL), and the mixture was stirred at 50°C for 1 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in CH₂Cl₂ (5 mL). The solution was made neutral with Et₃N at 0°C . Further Et₃N (0.306 mL, 2.20 mmol) and BzCl (0.080 mL, 0.692 mmol) were added to the stirred mixture at 0°C . The mixture was stirred at this temperature for 4.5 h, followed by quenching with H₂O. The whole was extracted with EtOAc. The extract was washed successively with 1 N HCl, H₂O and brine, and dried over Na₂SO₄. 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 (2:3) to give **9a** as a white solid (98.7 mg, 56% yield). Recrystallization from *n*-hexane–EtOAc gave pure **9a** as colorless crystals: mp $149\text{--}150^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -240.7$ (*c* 1.22, MeOH); IR (neat): 3340 (OH), 1963 (C=C=C), 1627 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 2.35 (t, *J* = 6.0 Hz, 1H), 3.85–3.93 (m, 2H), 4.92–4.99 (m, 1H), 5.61 (dd, *J* = 5.7, 4.6 Hz, 1H), 6.20 (dd, *J* = 5.7, 2.9 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 7.4,

7.4 Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 50.3, 62.7, 74.9, 100.7, 127.3 (2C), 128.2 (2C), 131.2, 134.4, 166.1, 200.8. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BrNO}_2$: C, 51.09; H, 4.29; N, 4.96. Found: C, 51.18; H, 4.22; N, 5.00.

2.1.4 (3a*S*,6a*S*)-6-Methylene-2-phenyl-3a,4,6,6a-tetrahydrofuro[3,4-*d*]oxazole (8)

To a stirred mixture of **9a** (40 mg, 0.142 mmol) in THF/MeOH (1.2 mL, 10:1) were added $\text{Pd}(\text{PPh}_3)_4$ (8.2 mg, 0.0071 mmol) and Cs_2CO_3 (55.5 mg, 0.170 mmol) at room temperature under argon (Table 2.1, Entry 6). The mixture was stirred at 50 °C for 2.5 h, and filtered through a short pad of silica gel with EtOAc to give a crude **8**. 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 (3:1) to give **8** as a white solid (25.5 mg, 89% yield): mp 98–99 °C; $[\alpha]_{\text{D}}^{25} +287.4$ (c 1.05, CHCl_3); IR (neat): 1641 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 4.32–4.37 (m, 2H), 4.43 (dd, $J = 2.0, 0.7$ Hz, 1H), 4.59–4.62 (m, 1H), 4.92 (ddd, $J = 8.0, 5.4, 2.9$ Hz, 1H), 5.42 (d, $J = 8.0$ Hz, 1H), 7.42 (dd, $J = 6.8, 6.8$ Hz, 2H), 7.50 (tt, $J = 6.8, 1.7$ Hz, 1H), 7.94 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.2, 76.2, 81.6, 87.5, 127.0, 128.4 (2C), 128.5 (2C), 131.7, 161.3, 164.2. *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.43; H, 5.70; N, 6.89.

2.1.5 (R)-N-[5-(Methoxymethyl)-2,3-dihydrofuran-3-yl]benzamide (13a)

Yellow oil; $[\alpha]_{\text{D}}^{26} -82.7$ (c 1.77, CHCl_3); IR (neat): 1634 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 3.42 (s, 3H), 4.00 (d, $J = 13.2$ Hz, 1H), 4.03 (d, $J = 13.2$ Hz, 1H), 4.32 (dd, $J = 10.3, 3.2$ Hz, 1H), 4.58 (dd, $J = 10.3, 8.6$ Hz, 1H), 5.09 (d, $J = 2.3$ Hz, 1H), 5.28–5.35 (m, 1H), 6.32 (d, $J = 6.3$ Hz, 1H), 7.42 (dd, $J = 7.4, 7.4$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.75 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 53.2, 59.0, 67.1, 77.4, 97.8, 126.9 (2C), 128.5 (2C), 131.6, 133.9, 159.9, 166.8; HRMS (FAB) calcd $\text{C}_{13}\text{H}_{16}\text{NO}_3$: $[\text{M}+\text{H}]^+$, 234.1130; found: 234.1130.

2.1.6 (R)-N-{5-[(2,2,2-Trifluoroethoxy)methyl]-2,3-dihydrofuran-3-yl}benzamide (13b)

Pale yellow solid; mp 100–101 °C; $[\alpha]_{\text{D}}^{27} -87.9$ (c 1.16, CHCl_3); IR (neat): 1629 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 3.91 (q, $J_{\text{C-F}} = 8.6$ Hz, 2H), 4.22 (s, 2H), 4.32 (dd, $J = 10.3, 3.2$ Hz, 1H), 4.58 (d, $J = 10.3, 8.6$ Hz, 1H), 5.14 (d,

$J = 2.9$ Hz, 1H), 5.29–5.36 (m, 1H), 6.38 (d, $J = 6.9$ Hz, 1H), 7.42 (dd, $J = 7.4$, 7.4 Hz, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.76 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 53.1, 66.7, 68.1 (q, $J_{\text{C-F}} = 34.8$ Hz), 77.5, 98.9, 123.8 (q, $J_{\text{C-F}} = 278.3$ Hz), 126.9 (2C), 128.6 (2C), 131.7, 133.8, 158.5, 166.9; ^{19}F NMR (471 MHz, CFCl_3) δ -74.0 (3F). *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 56.05; H, 4.82; N, 4.50.

2.1.7 *N*-(5-Methylfuran-3-yl)benzamide (14)

Yellow solid; mp 128–130 °C; IR (neat): 1643 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 2.29 (s, 3H), 6.04 (s, 1H), 7.42 (dd, $J = 7.7$, 7.7 Hz, 2H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.67 (s, 1H), 7.83 (d, $J = 7.7$ Hz, 2H), 8.00 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.6, 101.0, 124.7, 126.9 (2C), 128.7 (2C), 131.0, 131.8, 134.0, 151.1, 164.8; HRMS (FAB) calcd $\text{C}_{12}\text{H}_{12}\text{NO}_2$: $[\text{M}+\text{H}]^+$, 202.0868; found: 202.0864.

2.1.8 *tert*-Butyl (*R*)-4-[(*S*)-3-Bromopropa-1,2-dienyl]-2,2-dimethyloxazolidine-3-carboxylate (12b)

By a procedure identical with that described for synthesis of **12a** from **11a**, the propargylic alcohol **11b** (1.82 g, 7.13 mmol) was converted into **12b** as a colorless oil (902 mg, 40% yield): $[\alpha]_{\text{D}}^{25} +34.5$ (c 1.30, CHCl_3); IR (neat): 1962 (C=C=C), 1697 (C=O); ^1H NMR (500 MHz, CDCl_3 , 50 °C) δ 1.49 (s, 9H), 1.51 (s, 3H), 1.60 (s, 3H), 3.89 (dd, $J = 8.9$, 1.1 Hz, 1H), 4.06 (d, $J = 8.9$, 6.0 Hz, 1H), 4.36–4.65 (m, 1H), 5.40–5.55 (m, 1H), 6.05–6.11 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3 , 50 °C) δ 23.7 (0.5C), 24.9 (0.5C), 26.5 (0.5C), 27.2 (0.5C), 28.5 (3C), 55.5, 67.8, 74.3, 80.4, 94.4, 101.0, 151.8, 201.8; HRMS (FAB) calcd $\text{C}_{13}\text{H}_{21}\text{BrNO}_3$: $[\text{M}+\text{H}]^+$, 318.0705; found: 318.0708.

2.1.9 *N*-[(2*R*,4*S*)-5-Bromo-1-hydroxypenta-3,4-dien-2-yl]benzamide (9b)

By a procedure identical with that described for synthesis of **9a** from **12a**, the bromoallene **12b** (841 mg, 2.64 mmol) was converted into **9b** as a white solid (510 mg, 68% yield, dr = 10:1). Recrystallization from *n*-hexane–EtOAc gave **9b** (dr = 90:10) as colorless crystals: mp 110–111 °C; $[\alpha]_{\text{D}}^{26} +248.4$ (c 1.18, MeOH, dr = 90:10); IR (neat): 3323 (OH), 1960 (C=C=C), 1639 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 2.44 (t, $J = 6.0$ Hz, 1H), 3.89 (dd, $J = 5.4$, 4.3 Hz, 2H), 4.89–4.97 (m, 1H), 5.60 (dd, $J = 5.7$, 4.9 Hz, 1H), 6.22 (dd, $J = 5.7$, 2.9 Hz, 1H), 6.62 (d, $J = 6.3$ Hz, 1H), 7.45 (dd, $J = 7.4$, 7.4 Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 49.9, 64.6, 75.6, 99.4,

127.1 (2C), 128.7 (2C), 131.9, 133.9, 167.8, 201.5. *Anal.* Calcd for $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96. Found: C, 50.89; H, 4.37; N, 4.69.

2.1.10 [(3*a*S,6*S*,6*a*S)-2-Phenyl-3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*]oxazol-6-yl]methanol (15)

To a stirred mixture of **8** (352 mg, 1.75 mmol) in THF (7 mL) were added 9-BBN (0.5 M solution in THF; 10.5 mL, 5.25 mmol) at 0 °C under argon. After stirring at this temperature for 30 min and at room temperature for additional 10 min, the mixture was cooled to 0 °C and quenched by the careful addition of 15% NaOH (5 mL) and 30% H_2O_2 (5 mL). The mixture was stirred at room temperature for 1.5 h, followed by quenching with saturated NH_4Cl . The whole was extracted with Et_2O . The extract was washed with 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– $EtOAc$ (1:6) to give **15** as a white solid (309 mg, 80% yield). Recrystallization from *n*-hexane– $EtOAc$ gave pure **15** as colorless crystals: mp 130–131 °C; $[\alpha]_D^{24} +51.4$ (*c* 1.03, $CHCl_3$); IR (neat): 3363 (OH), 1648 (C=O); 1H NMR (400 MHz, $CDCl_3$) δ 1.91 (dd, *J* = 7.3, 4.9 Hz, 1H), 3.81 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.85–3.90 (m, 1H), 3.90–4.03 (m, 2H), 4.19 (d, *J* = 10.0 Hz, 1H), 4.92 (dd, *J* = 7.7, 5.4 Hz, 1H), 5.13 (dd, *J* = 7.7, 3.8 Hz, 1H), 7.42 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.0, 72.8, 73.5, 82.8, 83.9, 126.8, 128.3 (2C), 128.4 (2C), 131.6, 164.3. *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 5.85; N, 6.38.

2.1.11 (3*a*S,6*S*,6*a*S)-2-Phenyl-6-tetradecyl-3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*]oxazole (16)

To a stirred mixture of **15** (735 mg, 3.35 mmol) and Et_3N (0.93 mL, 6.70 mmol) in CH_2Cl_2 (33 mL) was added Tf_2O (0.79 mL, 4.69 mmol) at –78 °C, and the mixture was stirred for 30 min. 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) to give a crude triflate, which was used without further purification. To a suspension of CuI (128 mg, 0.67 mmol) in THF (15 mL) was added dropwise a solution of $C_{13}H_{27}MgBr$ in THF (0.75 M; 12.1 mL, 9.05 mmol) at –78 °C under argon. The mixture was allowed to warm to 0 °C, and was stirred at this temperature for 10 min. To the mixture of the resulting cuprate was added dropwise a solution of the above triflate in THF

(28 mL) at $-78\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to $-10\text{ }^{\circ}\text{C}$. After stirring at this temperature for 30 min, 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 dried over Na_2SO_4 . Concentration under reduced pressure followed by flash chromatography over Chromatorex[®] with *n*-hexane– EtOAc (6:1) gave **16** as a white solid (1.00 g, 78% yield): mp $93\text{--}94\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{24} + 60.9$ (*c* 1.05, CHCl_3); IR (neat): 1651 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 0.88 (t, $J = 6.9$ Hz, 3H), 1.21–1.40 (m, 22H), 1.43–1.56 (m, 2H), 1.76 (dt, $J = 7.0, 7.0$ Hz, 2H), 3.62 (td, $J = 7.0, 4.0$ Hz, 1H), 3.72 (dd, $J = 10.3, 5.4$ Hz, 1H), 4.11 (d, $J = 10.3$ Hz, 1H), 4.83 (dd, $J = 7.7, 5.4$ Hz, 1H), 4.99 (dd, $J = 7.7, 4.0$ 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, 26.1, 28.7, 29.3, 29.5, 29.6 (6C), 29.7, 31.9, 72.6, 73.2, 83.6, 84.0, 127.3, 128.3 (4C) 131.4, 164.3. *Anal.* Calcd for $\text{C}_{25}\text{H}_{39}\text{NO}_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.76; H, 10.42; N, 3.51.

2.1.12 (3*aS*,6*S*,6*aS*)-2-Phenyl-6-(3-phenylpropyl)-3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*]oxazole (17*a*)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.2, Entry 1). To a suspension of CuI (6.9 mg, 0.036 mmol) in THF (0.9 mL) was added dropwise a solution of $\text{Ph}(\text{CH}_2)_2\text{MgCl}$ in THF (1.0 M; 0.90 mL, 0.90 mmol) at $-78\text{ }^{\circ}\text{C}$ under argon. The mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, 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 $-78\text{ }^{\circ}\text{C}$, and the mixture was allowed to warm to room temperature. After stirring 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 was 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– EtOAc (2:1) gave **17a** as a colorless oil (42.2 mg, 76% yield): $[\alpha]_{\text{D}}^{26} + 97.7$ (*c* 1.49, CHCl_3); IR (neat): 1650 (C=N); ^1H 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 $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 308.1651, found: 308.1655.

2.1.13 (3*aS*,6*aS*)-6-Ethyl-2-phenyl-3*a*,4,6, 6*a*-tetrahydrofuro[3,4-*d*]oxazole (17*b*)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.2, Entry 2). To a suspension of CuBr (5.2 mg, 0.036 mmol) in THF (1.6 mL) was added dropwise a solution of MeMgBr in Et₂O (3.0 M; 0.30 mL, 0.90 mmol) at 0 °C under argon. The mixture 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 (1.1 mL) at –30 °C. After stirring for 1.5 h at this temperature, the mixture was allowed to warm to room temperature. The mixture was stirred for 3.0 h at room temperature and quenched with saturated NH₄Cl and 28% NH₄OH. The whole was extracted with Et₂O and the extract was washed with H₂O and brine, and was dried over Na₂SO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:3) gave **17b** as a white waxy solid (32.0 mg, 82% yield): mp 56–57 °C; $[\alpha]_D^{26} +79.7$ (*c* 1.02, CHCl₃); IR (neat): 1650 (C=N); ¹H NMR (500 MHz, CDCl₃) δ 1.09 (t, *J* = 7.4 Hz, 3H), 1.74–1.86 (m, 2H), 3.56 (ddd, *J* = 6.9, 6.9, 3.4 Hz, 1H), 3.72 (dd, *J* = 9.7, 5.4 Hz, 1H), 4.11 (d, *J* = 9.7 Hz, 1H), 4.84 (dd, *J* = 7.4, 5.4 Hz, 1H), 5.00 (dd, *J* = 7.4, 3.4 Hz, 1H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 10.4, 22.0, 72.6, 73.2, 83.3, 85.3, 127.3, 128.3 (4C), 131.4, 164.3; *Anal.* Calcd for C₁₃H₁₅NO₂: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.58; H, 7.05; N, 6.38.

2.1.14 (3*aS*,6*aS*)-6-Isobutyl-2-phenyl-3*a*,4,6, 6*a*-tetrahydrofuro[3,4-*d*]oxazole (17*c*)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.2, Entry 3). To a solution of the above triflate and CuBr·Me₂S (7.4 mg, 0.036 mmol) in THF/Me₂S (2.1 mL, 20:1) was added dropwise a solution of *i*-PrMgCl in THF (1.5 M; 0.84 mL, 1.26 mmol) at –20 °C under argon. After stirring for 2.0 h at this temperature, the mixture was allowed to warm to 0 °C. The mixture was stirred for 1.0 h at this temperature and quenched with saturated NH₄Cl and 28% NH₄OH. The whole was extracted with Et₂O and the extract was washed with H₂O and brine, and was dried over Na₂SO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:3) and then over Chromatorex[®] with *n*-hexane–EtOAc (3:1) gave **17c** as a white solid (23.8 mg, 54% yield). Recrystallization from *n*-hexane–EtOAc gave pure **17c** as colorless

crystals: mp 79–80 °C; $[\alpha]_{\text{D}}^{26} +71.5$ (c 0.96, CHCl_3); IR (neat): 1650 (C=N); ^1H NMR (500 MHz, CDCl_3) δ 0.99 (d, $J = 6.3$ Hz, 3H), 1.00 (d, $J = 6.3$ Hz, 3H), 1.62 (ddd, $J = 13.7, 7.4, 6.7$ Hz, 1H), 1.69 (ddd, $J = 13.7, 7.4, 6.9$ Hz, 1H), 1.82–1.90 (m, 1H), 3.68–3.71 (m, 1H), 3.71 (dd, $J = 9.7, 5.4$ Hz, 1H), 4.11 (d, $J = 9.7$ Hz, 1H), 4.83 (dd, $J = 7.4, 5.4$ Hz, 1H), 4.98 (dd, $J = 7.4, 4.0$ Hz, 1H), 7.40 (dd, $J = 7.4, 7.4$ Hz, 2H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.93 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.6, 23.2, 25.3, 37.6, 72.7, 73.2, 82.3, 84.0, 127.3, 128.3 (4C), 131.4, 164.3. *Anal.* Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.19; H, 7.81; N, 5.60.

2.1.15 (3*aS*,6*S*,6*aS*)-6-(2-Methylallyl)-2-phenyl- -3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*]oxazole (17*d*)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.2, Entry 4). To a solution of the above triflate and $\text{CuBr}\cdot\text{Me}_2\text{S}$ (7.4 mg, 0.036 mmol) in THF/ Me_2S (1.0 mL, 9:1) was added dropwise a solution of $\text{CH}_2=\text{C}(\text{CH}_3)\text{MgBr}$ in THF (0.5 M; 1.8 mL, 0.90 mmol) at -20 °C under argon. After stirring for 2.0 h at this temperature, the mixture was allowed to warm to 0 °C. The mixture was stirred for 1.0 h at this temperature and 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 was dried over Na_2SO_4 . Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane– EtOAc (2:3) and then over Chromatorex[®] with *n*-hexane– EtOAc (3:1) gave **17d** as a white solid (28.8 mg, 66% yield): mp 55–56 °C; $[\alpha]_{\text{D}}^{26} +85.6$ (c 1.10, CHCl_3); IR (neat): 1650 (C=N); ^1H NMR (500 MHz, CDCl_3) δ 1.85 (s, 3H), 2.47 (dd, $J = 14.9, 7.4$ Hz, 1H), 2.52 (dd, $J = 14.9, 6.3$ Hz, 1H), 3.74 (dd, $J = 9.7, 5.4$ Hz, 1H), 3.81 (ddd, $J = 7.4, 6.3, 3.7$ Hz, 1H), 4.13 (d, $J = 9.7$ Hz, 1H), 4.84 (dd, $J = 7.7, 5.4$ Hz, 1H), 4.89–4.91 (m, 2H), 5.01 (dd, $J = 7.7, 3.7$ 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 22.9, 36.8, 72.6, 73.4, 82.2, 83.6, 112.6, 127.2, 128.3 (4C), 131.4, 141.9, 164.3. *Anal.* Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.77; H, 7.09; N, 5.64.

2.1.16 (1*S*,4*S*,7*S*)-5-(4-Phenylhepta-1,6-dien-4-yl)- -2-oxa-5-azabicyclo[2.2.1]heptan-7-ol (18)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.3, Entry 2). To a

mixture of allylMgBr in Et₂O (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 $-30\text{ }^{\circ}\text{C}$ under argon. After stirring for 1.5 h at this temperature, the mixture was quenched with saturated NH₄Cl. The whole was extracted with Et₂O and the extract was washed with H₂O and brine, and was dried over Na₂SO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:2) gave **18** as a colorless oil (46.5 mg, 91% yield): $[\alpha]_{\text{D}}^{25} +35.9$ (*c* 1.61, CHCl₃); IR (neat): 3445 (OH); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₂₄NO₂: [M+H]⁺, 286.1807, found: 286.1805.

2.1.17 (3*aS*,6*S*,6*aS*)-6-(*But-3-enyl*)-2-phenyl -3*a*,4,6,6*a*-tetrahydrofuro[3,4-*d*]oxazole (**17e**)

By a procedure identical with that described for synthesis of **16** from **15**, the alcohol **15** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification (Table 2.3, Entry 3). To a suspension of CuCN (71.6 mg, 0.72 mmol) in THF (2.0 mL) was added dropwise a solution of MeLi in Et₂O (1.06 M; 1.36 mL, 1.44 mmol) at $-78\text{ }^{\circ}\text{C}$ under argon. The mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$, and was stirred for 10 min at this temperature. To the mixture was added dropwise allyltributylstannane (0.45 mL, 1.44 mmol) at $-78\text{ }^{\circ}\text{C}$, 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 $-78\text{ }^{\circ}\text{C}$. After stirring for 30 min at this temperature, the mixture was quenched with saturated NH₄Cl and 28% NH₄OH. The whole was extracted with Et₂O and the extract was washed with H₂O and brine, and was dried over Na₂SO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1 to 2:3) gave **17e** as a white waxy solid (14.0 mg, 32% yield): mp $55\text{--}56\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{24} +91.7$ (*c* 0.50, CHCl₃); IR (neat): 1651 (C=N); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 $C_{15}H_{18}NO_2 [M+H]^+$, 244.1338, found: 244.1338.

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2012, XVI, 106 p., Hardcover

ISBN: 978-4-431-54042-7