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SYNTHETIC STUDIES ON HALICHLORINE AND PINNAIC ACID: PALLADIUM-MEDIATED CONSTRUCTION OF THE BICYCLIC SPIRO CORE[1]

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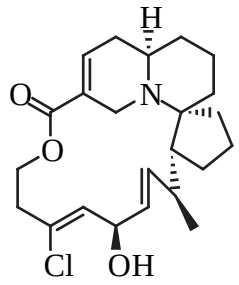
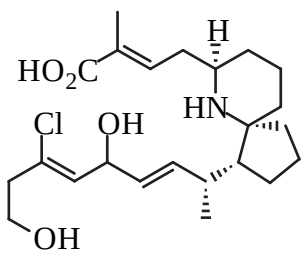
Abstract - Palladium-mediated cyclization of **19** and **23** directed toward the construction of the bicyclic core (**3**), which would serve as a key intermediate for the total synthesis of halichlorine (**1**) and pinnaic acid (**2**), was explored and found to proceed for **19** in a highly diastereoselective manner furnishing the unnatural isomer (**21**), and providing a mixture of the desired product (**3**) and (**21**) for **23**.

The alkaloids halichlorine (**1**)[2] and pinnaic acid (**2**),[3] isolated in 1996 by Uemura and coworkers from the marine sponge *Halichondria okadai* and the Okinawan *Pinna muricata*, have attracted considerable interest because of their significant biological profiles as potent inhibitors of VCAM-1 induction in cultured human umbilical vein endothelial cells[2] and as specific inhibitors of phospholipase A_2.[3] The most intriguing and common structural feature of these unique alkaloids is the spirocyclic core, which has three stereogenic centers. Their unusual structures coupled with their promising biological activities, especially as potential leads for anti-atherosclerotic drugs, have inspired numerous efforts directed toward their synthesis.[2b, 4] Consequently, a variety of approaches to the spirocyclic core moiety have been recorded,[4b-h] and the total synthesis of halichlorine has been reported by Danishefsky.[5]



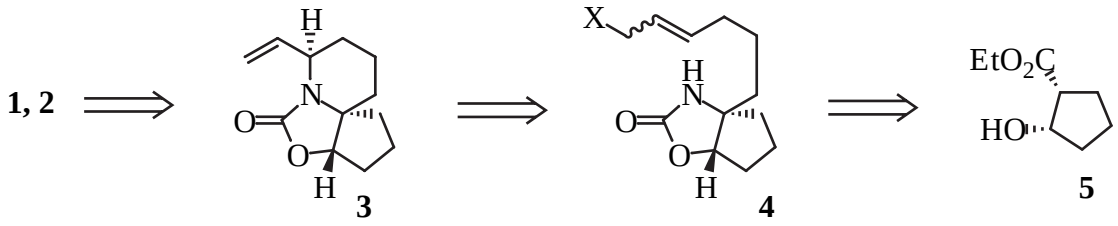
halichlorine (**1**)

Figure 1



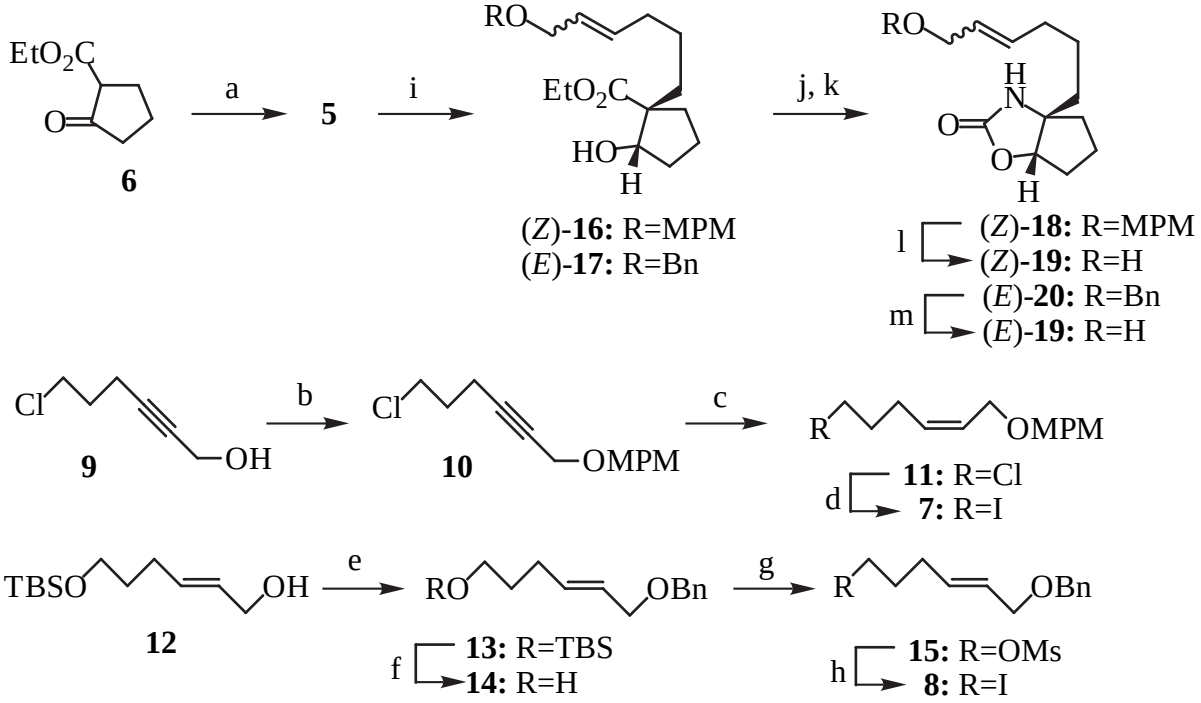
pinnaic acid (**2**)

In this context, we targeted the spirocyclic core (**3**) as a potentially versatile intermediate because it contains the requisite absolute stereogenic centers as well as appropriate functional handles for introducing the remaining substituents and side chains of the alkaloids. We envisaged that this compact intermediate (**3**) might be assembled *via* the palladium-catalyzed cyclization[6] of the alkenyl bicyclic carbamate (**4**), which would be derived from a optically active (1*S*, 2*R*)-carbethoxycyclopentanol (**5**)[7a] (Scheme 1). We now report the implementation of such a cyclization as the key step in an attempted enantioselective synthesis of **3**.

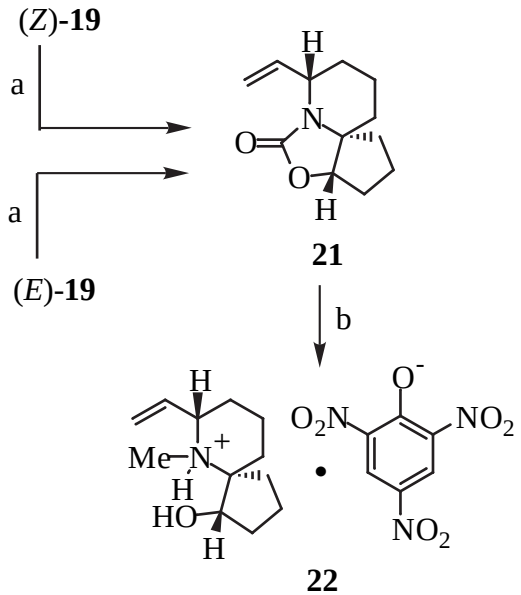


Scheme 1. Retrosynthetic analysis

Baker's yeast-mediated reduction[8] of 2-carbethoxycyclopentanone (**6**) produced (1*S*, 2*R*)-carbethoxycyclopentanol (**5**)[7a] with >99% ee in 63% yield. Alkylation of the dianion[7b] of **5** with the alkenyl iodides (**7** and **8**) with *Z* and *E* double bonds, which were prepared from the propargyl alcohol (**9**) and the allyl alcohol (**12**) *via* standard functional group transformations in 67 and 87% overall yields, respectively, provided (*Z*)-**16** and (*E*)-**17** in 59 and 75% yields, respectively. After hydrolysis of the ester moiety, the resulting hydroxy acids were treated with diphenylphosphoryl azide[9] in refluxing benzene to give the cyclic carbamates ((*Z*)-**18**) and ((*E*)-**20**) in 65 and 82% yields, respectively, for the two steps. The alcohols ((*Z*)-**19**) and ((*E*)-**19**), the substrates for the palladium-catalyzed cyclization, were obtained by independent deprotection of (*Z*)-**18** with cerium ammonium nitrate (CAN) and of (*E*)-**20** with Birch reduction (Scheme 2). With the substrates in hand, we initially examined the Pd(II)-catalyzed cyclization[10] of (*Z*)-**19** and (*E*)-**19**. When the alcohol ((*Z*)-**19**) was treated with a catalytic $PdCl_2(PhCN)_2$ in THF at room temperature, the cyclization proceeded smoothly and a tricyclic product was obtained as a single diastereomer in 56% yield. Since the stereostructure of the product could not be determined spectroscopically at this stage, it was reduced with $LiAlH_4$ and the resulting *N*-methyl derivative was then converted into the crystalline picrate (**22**). The structure, including stereochemistry, was established by single crystal X-Ray analysis as shown in Figure 2, and indicated that the stereochemistry at C_5 in **21** was opposite to that desired. Similarly, the cyclization of (*E*)-**19** under the same reaction conditions as for the



Scheme 2. ***Reagents and Conditions:*** a, Baker's yeast, H_2O, 30 °C, 63%; b, MPMCl, NaH, $^nBu_4NI$, THF, rt, 84%; c, H_2, Lindlar cat., quinoline, hexane, rt, 89%; d, NaI, acetone, reflux, 90%; e, BnBr, NaH, THF, rt, 97%; f, $^nBu_4NF$, THF, rt, 96%; g, MsCl, Et_3N, CH_2Cl_2, rt; h, LiI, acetone, reflux, 93% (2 steps); i, LDA, THF, HMPA, (*Z*)- and (*E*) $I(CH_2)_3CH{=}CHCH_2OMPM$ **7** and **8**, -45 °C, 59% for (*Z*)-**15**, 75% for (*E*)-**16**; j, 10% KOH (aq.), rt; k, $(PhO)_2PON_3$, benzene, reflux, 65% (2 steps) for (*Z*)-**17**, 82% (2 steps) for (*E*)-**19**; l, CAN, aq. MeCN, rt, 86%; m, Li, liq. NH_3, -78 °C, 77%.



Scheme 3. ***Reagents and Conditions:*** a, $PdCl_2(PhCN)_2$ (0.3 eq.), THF, rt, 62% for (*Z*), 42% for (*E*); b, $LiAlH_4$, THF, rt, 62%; then picric acid, rt and recrystallized from $MeCN/Et_2O$.

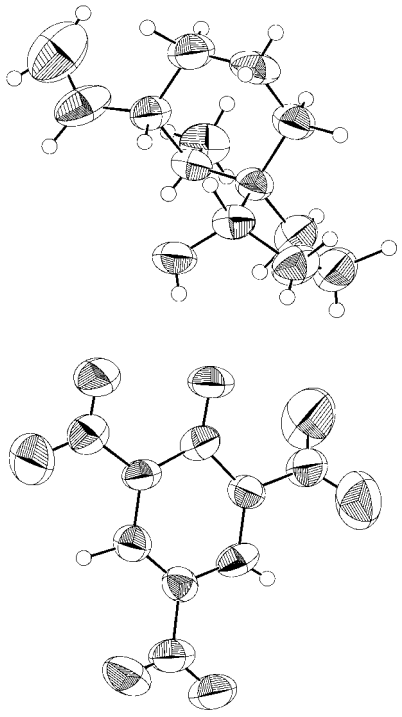
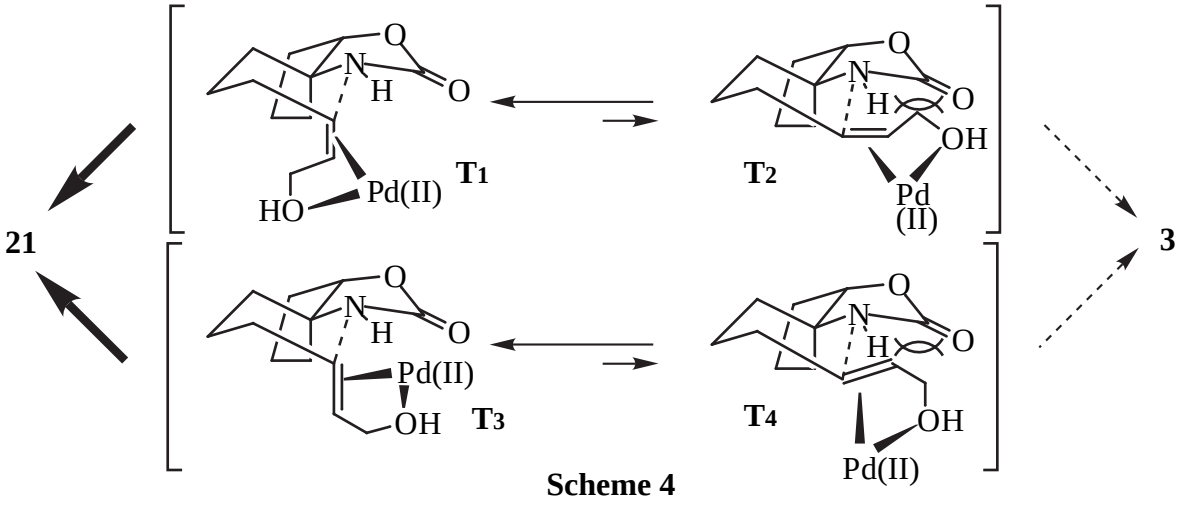


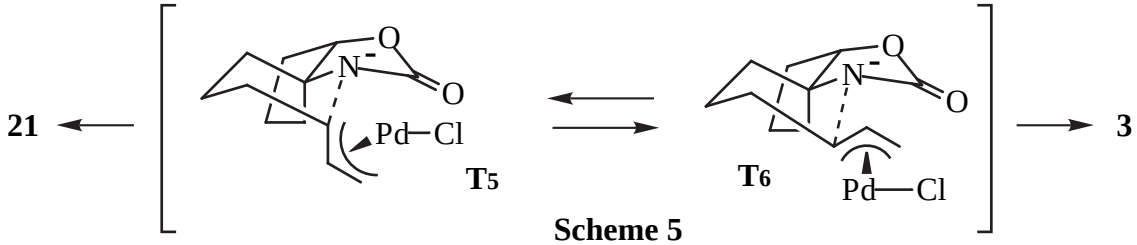
Figure 2. ORTEP drawing of the X-Ray structure of **22**

Z-isomer also provided **21** as a single product in 46% yield. The results might be rationalized by considering that the reaction would prefer transition states T_1 and T_3, which provide access to the undesired isomer (**21**), to the sterically congested transition states T_2 and T_4 leading to the formation of the desired product (**3**), as shown in Scheme 4.



Scheme 4

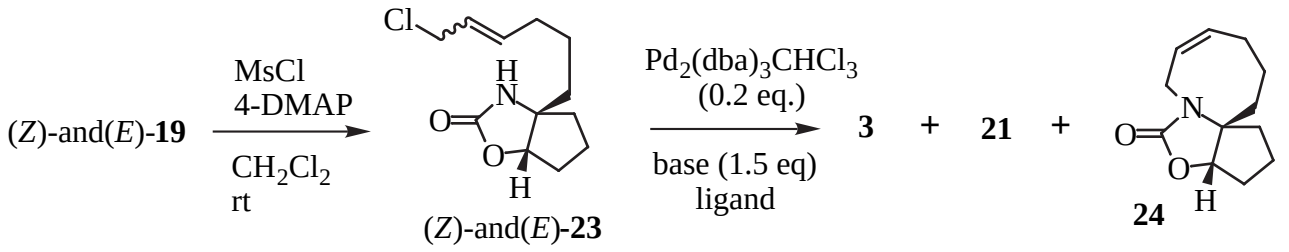
Disappointed by the failure to prepare **3** selectively, we next turned our attention to the Pd(0)-catalyzed cyclization.[11] It was expected that the non-bonding interactions would decrease in the transition state (**T6**) and the desired isomer (**3**) would be generated preferentially (Scheme 5).



Scheme 5

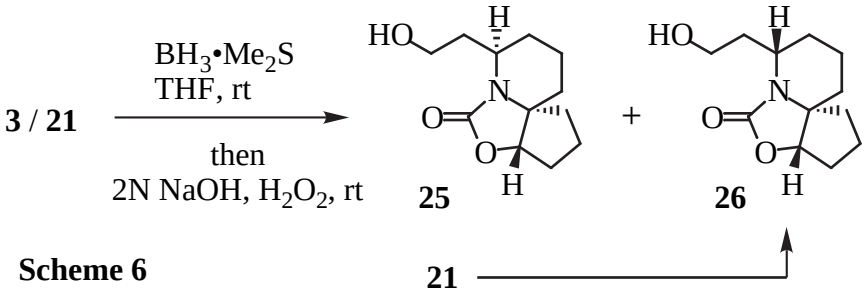
Treatment of the allyl chloride ((*Z*)-**23**), which was prepared from (*Z*)-**19** with mesyl chloride and 4-DMAP, with catalytic $Pd_2(dba)_3CHCl_3$, NaH and triphenylphosphine in THF at room temperature afforded an inseparable 1:1 mixture of **3** and the C_5-epimer (**21**) in 50% yield (Table 1, entry 1). Encouraged by this result, we explored the optimum conditions for the cyclization of (*Z*)-**23** (entries 2-4) and (*E*)-**23** (entries 5, 6) producing **3** predominantly. The results are shown in Table 1. However, in no case could the preferential formation of **3** be achieved. It should be noted that when the reaction was conducted in DMF, the tricyclic carbamate (**24**) with an eight-membered nitrogen heterocycle was obtained in 90% yield[12] (entry 3). The selectivity in the cyclization could be attributed to the small difference in the energy between the transition states T_5 and T_6 (Scheme 5).

Table 1. Pd(0)-catalyzed cyclization of (*Z*)- and (*E*)-**18**



entry	substrate	base	ligand	solvent	reaction time (h)	yield (%)	products ratio **3 : 21 : 24**
1	(*Z*)-**23**	NaH	Ph_3P	THF	4	50	1 : 1 : 0
2	(*Z*)-**23**	NaH	$Ph_2P(CH_2)_3PPh_2$	THF	5	74	1 : 1.5 : 0
3	(*Z*)-**23**	NaH	Ph_3P	DMF	1.5	90	0 : 0 : 1
4	(*Z*)-**23**	KH	$Ph_2P(CH_2)_3PPh_2$	THF	4	82	1 : 1.5 : 0
5	(***E***)-**23**	NaH	Ph_3P	THF	4	28	1 : 2 : 0
6	(***E***)-**23**	KH	$Ph_2P(CH_2)_3PPh_2$	THF	2	76	1 : 1.5 : 0

Since the structure of **3** could not be confirmed at this stage due to the difficulty of separation, the mixture was subjected to a hydroboration/oxidation reaction to give a chromatographically separable mixture of alcohols (**25**) and (**26**) in 72% yield. The alcohol (**26**) was identical with a compound which was prepared from the structurally established **21** by the same treatment, and the other alcohol (**25**) was determined to be the C_5-epimer. The alcohol (**25**) would be useful as an advanced intermediate for the total syntheses of the target alkaloids (Scheme 6).



Scheme 6

In summary, we examined the palladium-mediated cyclization of **19** and **23** directed toward the construction of the bicyclic core (**3**), which would serve as a key intermediate for the total synthesis of halichlorine (**1**) and pinnaic acid (**2**). We found that it proceeded in a highly diastereoselective manner furnishing the unnatural isomer (**21**) for **19** and providing a mixture of the desired product (**3**) and (**21**) for **23**. We are now studying another diastereoselective cyclization leading to **3** or to its congener by using the optically pure bicyclic carbamate (**19**).

ACKNOWLEDGEMENT

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EXPERIMENTAL

Materials. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Butyllithium, purchased from Kanto Chemical Co., Inc., was titrated with diphenylacetic acid. Ethyl 2-oxocyclopentanecarboxylate was commercially available.

General Procedures. ^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using Bruker AM400 and JEOL GSX400 (400 MHz) spectrometers, unless otherwise noted. ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) using Brucker AM400 (100 MHz), JEOL GSX400 (100 MHz) and JEOL AL300 (75 MHz) spectrometers. IR spectra were recorded on JASCO FT/IR-410 spectrophotometer. MS spectra were obtained on a JEOL GX303. Column chromatography was performed on silica gel, FUJI SILYSIA CHEMICAL BW-127ZH (100-270 mesh). Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60 F_{245}). Melting points were measured with a Büchi 535 melting point apparatus and are uncorrected. All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. Solutions of alkyllithium reagents were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa.

(*1R,2S*)-Ethyl 2-hydroxycyclopentanecarboxylate (5)[7]: Baker's yeast (126 g) was added to a stirred tap water (1 L) at 30 ˚C. After 50 min, ethyl 2-oxocyclopentanecarboxylate (5.00 g, 32 mmol) was added and the suspension was stirred for 20 h at 30 ˚C. The mixture was diluted with acetone (1 L) and filtered through celite. After concentration *in vacuo*, the residue was extracted with EtOAc (3 x 500 mL) and the organic phase was washed with brine (500 mL), dried over $MgSO_4$ and concentrated to give a brown oil (3.44 g). Column chromatography (10% EtOAc/hexane) gave 3.17 g (63%) of **5** as a colorless oil.

6-Chloro-1-(4-methoxyphenyl)methoxy-2-hexyne (10): To a suspension of NaH (62.5% in mineral oil, 1.9 g, 49 mmol, washed with hexane) in THF was added a solution of **9**[13] (4.29 g, 32 mmol) in THF (16 mmol) at 0 ˚C. After 40 min, 4-methoxybenzyl chloride (5.4 mL, 39 mmol) and tetrabutylammonium iodide (358 mg, 0.97 mmol) were added and the mixture was stirred for 5 h at rt. The resulting mixture was quenched with water (50 mL) and extracted with EtOAc (3 x 100 mL), and the extract was washed with water (100 mL) and brine (100 mL), and dried over $MgSO_4$. The solvent was evaporated

to give a yellow oil (8.97 g), which was chromatographed (10% ether/hexane) over silica gel to afford **10** (6.89 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.98 (tt, *J* = 6.4, 6.8 Hz, 2H), 2.43 (ddt, 2H, *J* = 1.8, 2.3, 6.8 Hz), 3.66 (t, *J* = 6.4 Hz, 2H), 3.81 (s, 3H), 4.12 (dd, *J* = 1.8, 2.3 Hz, 2H), 4.51 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 16.17, 31.20, 43.59, 55.20, 57.19, 71.07, 77.03, 84.88, 113.75, 129.51, 129.66, 159.29; IR (neat) 2222, 1612 cm^{-1}; MS (EI) m/z: 252 (M^+), 251 (M^+ - 1), 253 (M^+ + 1), 254 (M^+ + 2); HRMS calcd for $C_{14}H_{17}O_2Cl$ 252.0917, found 252.0914.

(*Z*)-6-Chloro-1-(4-methoxyphenyl)methoxy-2-hexene (11): A solution of **10** (6.89 g, 27 mmol) in hexane (100 mL) was hydrogenated over Lindlar catalyst (2.10 g) in the presence of quinoline (6.80 mL, 57 mmol) under H_2 atmosphere (1 atm) and the mixture was stirred for 20 h at rt. After filtration, the filtrate was concentrated *in vacuo* to give a residue which was chromatographed (10% ether/hexane) over silica gel column to give 6.19 g (89%) of **11** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.83 (tt, *J*=6.4, 7.5 Hz, 2H), 2.21 (dd, *J* = 7.2, 7.3 Hz, 2H), 3.52 (dd, *J* = 6.6, 6.8 Hz, 2H), 3.80 (s, 3H), 4.06 (d, *J* = 6.4 Hz, 2H), 4.45 (d, *J* = 5.9 Hz, 2H), 5.53 (m, 1H), 5.66 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 24.72, 32.11, 44.29, 55.27, 65.34, 71.92, 113.77, 127.85, 129.42, 130.36, 131.40, 159.19; IR (neat) 1613 cm^{-1}; MS (EI) m/z: 254 (M^+), 253 (M^+ - 1), 255 (M^+ + 1), 256 (M^+ + 2); HRMS calcd for $C_{14}H_{19}O_2Cl$ 254.1074, found 254.1062.

(*Z*)-6-Iodo-1-(4-methoxyphenyl)methoxy-2-hexene (7): To a solution of **11** (6.19 g, 24 mmol) in acetone (130 mL) was added NaI (18.17 g, 120 mmol), and the mixture was refluxed for 26 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed (40% benzene/hexane then EtOAc) over silica gel column to give 7.55 g (90%) of **7** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.88 (tt, *J* = 6.8, 7.2 Hz, 2H), 2.16 (dt, *J* = 6.8, 7.2 Hz, 2H), 3.17 (t, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 4.07 (d, *J* = 6.4 Hz, 2H), 4.45 (s, 2H), 5.53 (dt, *J* = 10.9, 7.3 Hz, 1H), 5.64 (dt, *J* = 10.9, 6.8 Hz, 1H), (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 6.25, 28.12, 32.83, 55.09, 65.31, 71.75, 113.59, 127.78, 129.24, 130.17, 130.90, 158.99; IR (neat) 1612 cm^{-1}; MS (EI) m/z: 346 (M^+), 347 (M^+ + 1), 315 (M^+ - MeO); HRMS calcd for $C_{14}H_{19}O_2I$ 346.0430, found 346.0425.

(*E*)-1-Benzyloxy-6-(*tert*-butyldimethylsilyloxy)-2-hexene (13): To a suspension of NaH (62.7% in mineral oil, 8.80 g, 225 mmol) in THF (300 mL) was added a solution of **12**[14] (25.95 g, 112.6 mmol) in THF (100 mL) at 0 ˚C. After the mixture was stirred for 1.5 h, benzyl bromide (34 mL, 281.6 mmol) was added and the reaction mixture was stirred for 16.5 h at rt. The mixture was quenched with saturated NH_4Cl aq. (100 mL) and extracted with EtOAc (4 x 100 mL). The extracts were washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$. After removal of the solvent *in vacuo* , the residue was chromatographed (hexane then 5% EtOAc/hexane) over silica gel column to afford 35.15 g

(97%) of **13** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6H), 0.89 (s, 9H), 1.61 (tt, *J* = 6.4, 7.3 Hz, 2H), 2.12 (dt, *J* = 6.4, 7.3 Hz, 2H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.97 (d, *J* = 5.9 Hz, 2H), 4.50 (s, 2H), 5.63 (dt, *J* = 5.9, 15.5 Hz, 1H), 5.71 (dt, *J* = 6.4, 15.5 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: -5.30, 18.31, 25.94, 28.60, 32.17, 62.52, 70.88, 71.85, 126.49, 127.50, 127.74, 128.32, 134.35, 138.44; IR (neat)1670 cm^{-1}; MS (FAB) m/z: 343 (M^++ Na), 320 (M^+) 319 (M^+ - 1), 263 (M^+ - ^{t}Bu); HRMS (FAB) calcd for $C_{19}H_{32}O_2NaSi$ (M^++ Na) 343.2069, found 343.2078.

(*E*)-6-Benzyloxy-4-hexen-1-ol (14): To a solution of **13** (100 mg, 0.31 mmol) in THF (2 mL) was added tetrabutylammonium fluoride solution (1 M in THF, 0.31 mmol) at 0 ˚C and the mixture was stirred for 15 h at rt. After addition of water, the mixture was extracted with EtOAc (5 x 30 ml) and the extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil (90 mg). Column chromatography (20% EtOAc/hexane) gave 62 mg (96%) of **14** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.65 (ddt, *J* = 6.4, 7.3, 8.0 Hz, 2H + 1H (OH)), 2.14 (dt, *J* = 7.3, 8.0 Hz, 2H), 3.63 (dd, *J* = 6.4, 7.2 Hz, 2H), 3.97 (d, *J* = 5.9 Hz, 2H), 4.50 (s, 2H), 5.65 (dt, *J* = 5.9, 16.4 Hz, 1H), 5.71 (dt, *J* = 6.4, 15.0 Hz, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 28.55, 31.89, 62.22, 70.74, 71.93, 126.78, 127.52, 127.74, 128.31, 133.89, 138.28; IR (neat) 3398, 1674 cm^{-1}; MS (EI) m/z: 206 (M^+), 115 (M^+- Bn); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1299.

(*E*)-1-Benzyloxy-6-iodo-2-hexene (8): To a solution of **14** (1.36 g, 6.58 mmol) in CH_2Cl_2 (25 mL) were added triethylamine (1.83 mL, 13.2 mmol) and mesyl chloride (0.76 mL, 9.87 mmol) at 0 ˚C and the mixture was stirred for 1.5 h at rt. Saturated $NaHCO_3$ was added and then the mixture was extracted with CH_2Cl_2. The organic phase was washed with 5% HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. After concentration *in vacuo*, the residue (1.94 g of a dark yellow oil) was dissolved in acetone (45 mL) and LiI (4.45 g, 33 mmol) was added. The mixture was refluxed for 0.5 h, and then concentrated *in vacuo*. Water was added to the mixture, which was, then, extracted with CH_2Cl_2. The organic layer was washed with saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give brown oil (2.12 g). Column chromatography (5% EtOAc/hexane) gave 1.94 g (93%) of **13** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.92 (tt, *J* = 6.8, 7.3 Hz, 2H), 2.18 (m, 2H), 3.18 (t, *J* = 6.8 Hz, 2H), 4.00 (d, *J* = 2.7 Hz, 2H), 4.50 (s, 2H), 5.67 (m, 2H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 6.26, 32.55, 32.86, 70.64, 72.06, 127.57, 127.75, 127.88, 128.36, 131.96, 138.29; IR (neat) 1671 cm^{-1}; MS (EI) m/z: 316 (M^+), 225 (M^+- Bn); HRMS calcd for $C_{13}H_{17}OI$ 316.0324, found 316.0316.

(*1R,2S,Z*)-Ethyl 2-hydroxy-1-[6-(4-methoxyphenylmethoxy)-4-hexenyl]cyclopentane-1-carboxylate (16): To a THF solution of LDA, prepared from diisopropylamine (2.53 mL, 18.0 mmol) and butyllithium (1.6 M in hexane, 10.7 mL, 17.2 mmol) at –78 ˚C in THF (20 mL), was added a solution of **5** (1.29 g, 8.20 mmol) in THF (7.5 mL) dropwise, and the mixture was stirred for 0.5 h at –45 ˚C. A solution of **7** (3.11 g, 8.98 mmol) in THF (4.5 mL) and HMPA (4.5 mL) was added and the mixture was

stirred for 1 h at the same temperature. Saturated NH_4Cl aq was added and the mixture was extracted with EtOAc (4 x 100 mL). The combined organic layer was washed with saturated $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a pale yellow oil (4.24 g). Column chromatography (10% then 30% EtOAc/hexane) gave 1.81 g (59%) of **16** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, *J* = 6.8 Hz, 3H), 1.35-2.22 (m, 10H), 3.81 (d, *J* = 2.3 Hz, 3H), 3.99 (m, 1H), 4.01 (d, *J* = 6.4 Hz, 2H), 4.18 (q, *J* = 7.3 Hz, 2H), 4.43 (s, 2H), 5.53 (dt, *J* = 6.8, 11.2 Hz, 1H), 5.60 (dt, *J* = 6.4, 10.9 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ:14.24, 20.32, 25.02, 27.77, 31.38, 32.17, 35.90, 55.22, 58.14, 60.53, 65.34, 71.75, 79.13, 113.72, 126.68, 129.32, 130.37, 132.85, 159.13, 176.17; IR (neat) 3461, 1716, 1612 cm^{-1}; MS (EI) m/z: 376 (M^+); HRMS calcd for $C_{20}H_{32}O_5$ 376.2250, found 376.2281; $[\alpha]_D^{24}$+15.8° (c 1.04, $CHCl_3$).

(*1R,2S,E*)-Ethyl 2-hydroxy-1-(6-benzyloxy-4-hexenyl)cyclopentane-1-carboxylate (17): To a THF solution of LDA, prepared from diisopropylamine (9.00 mL, 64.0 mmol) and butyllithium (1.6 M in hexane, 40 mL, 60 mmol) at –78 ˚C in THF (92 mL), was added a solution of **5** (4.60 g, 29.0 mmol) in THF (34 mL) dropwise, and the mixture was stirred for 1 h at –45 ˚C. A solution of **8** (10.1 g, 32.0 mmol) in THF (20 mL) and HMPA (20 mL) was added and the mixture was stirred for 6.5 h at the same temperature. Saturated NH_4Cl aq (100 mL) was added and the mixture was extracted with EtOAc (4 x 100 mL). The combined organic layer was washed with saturated $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a dark red oil (14.44 g). Column chromatography (10% benzene/chloroform then 10% EtOAc/chloroform), followed by distillation (bp 70 ˚C / 2 mmHg), gave 7.59 g (75%) of **17** as a brownish oil. ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, *J* = 7.3 Hz, 3H), 1.35-2.22 (m, 12H), 2.90 (br s, 1H, D_2O exchangeable), 3.96 (d, *J* = 5.5 Hz, 2H), 4.01 (t, *J* = 5.0 Hz, 1H), 4.19 (q, *J* = 7.3 Hz, 2H), 4.50 (s, 2H), 5.61 (dt, *J* = 5.9, 15.5 Hz, 1H), 5.65 (dt, *J* = 6.4, 15.5 Hz, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 14.15, 20.27, 24.49, 31.14, 32.11, 32.45, 35.80, 58.18, 60.43, 70.65, 71.78, 79.09, 126.67, 127.42, 127.63, 128.22, 133.84, 138.24, 176.06; IR (neat) 3480, 1731 cm^{-1}; MS (FAB) m/z: 347 (M^+), 239 (M^+- BnOH); HRMS calcd for $C_{21}H_{31}O_4$ (M^++ 1) 347.2222, found 347.2238; $[\alpha]_D^{24}$ +17.6° (c 1.17, $CHCl_3$).

(*1S,5R, Z*)-5-(6-(4-Methoxyphenyl)methoxy-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one (18): A solution of **16**(3.85 g, 10 mmol) in ethanol (65 mL) and 10% KOH aq (63 mL) was stirred for 27 h at rt. After concentration, ether was added and the mixture was extracted with water (3 x 50 mL). The aqueous solution was acidified by 5% HCl aq at 0 ˚C. The mixture was extracted with ether (4 x 50 mL) and the organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated to give 3.32 g of the crude carboxylic acid. The acid was dissolved in benzene (100 mL) and diphenylphosphoryl azide (2.67 mL, 12.4 mmol) and triethylamine (1.73 mL, 12.4 mmol) were added. After being refluxed for 1 h, the mixture was treated with water and extracted with EtOAc. The organic

layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 4.24 g of crude products, which was purified with column chromatography (20% EtOAc/hexane) to give **18** (2.28 g, 65%) as a colorless oil. ^1H NMR ($CDCl_3$) δ:1.60-1.90 (m,10H), 2.10 (m, 2H), 3.80 (s, 3H), 4.01 (d, *J* = 6.4 Hz, 2H), 4.44 (s, 2H), 4.55 (d, *J* = 5.5 Hz, 1H), 5.50 (br s, 1H, D_2O exchangeable), 5.55-5.65 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.40, 24.18, 27.40, 33.86, 38.65, 39.06, 55.23, 65.27, 68.21, 71.82, 86.46, 113.72, 126.96, 129.38, 130.32, 132.66, 159.14, 159.64; IR(neat) 3271, 1746, 1613 cm^{-1}; MS (EI) m/z: 345 (M^+); HRMS calcd for $C_{20}H_{27}NO_4$ 345.1940, found 345.1926; $[\alpha]_D^{26}$ -27.1° (c 2.83, $CHCl_3$).

(*1S,5R,E*)-5-(6-Benzyloxy-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one (20): A solution of **17** (13.92 g, 40.18 mmol) in ethanol (248 mL) and 10% KOH aq (248 mL) was stirred for 13 h at rt. After concentration, ether was added and the mixture was extracted with water (3 x 50 mL). The aqueous solution was acidified by 5% HCl aq at 0 ˚C. The mixture was extracted with ether (5 x 100 mL) and the organic layer was washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated to give 12.97 g of the crude carboxylic acid. The acid was dissolved in benzene (400 mL), and diphenylphosphoryl azide (11.4 mL, 53 mmol) and triethylamine (7.4 mL, 53 mmol) were added. After being refluxed for 5.5 h, the mixture was treated with water and extracted with EtOAc (4 x 100 mL). The organic layer was washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give 18.46 g of crude products, which was purified with column chromatography (20% EtOAc/hexane) to give **20** (10.62 g, 84%) as a colorless oil. ^1H NMR ($CDCl_3$) δ: 1.60-1.90 (m, 10H), 2.10 (dt, *J* = 6.4, 14.1 Hz, 2H), 3.97 (d, *J* = 5.5 Hz, 2H), 4.50 (s, 2H), 4.57 (d, *J* = 5.9 Hz, 1H), 5.14 (m, 1H, D_2O exchangeable), 5.62 (dt, *J* = 5.5, 15.5 Hz, 1H), 5.68 (dt, *J* = 5.9,15.5 Hz, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 23.05, 23.89, 32.24, 33.91, 38.79, 39.20, 68.10, 70.72, 72.12, 86.49, 127.31, 127.59, 127.76, 128.37, 133.36, 138.30, 159.18; IR (neat) 3267, 1745 cm^{-1}; MS (FAB) m/z: 316 (M^+), 208 (M^+- BnOH); HRMS (FAB) calcd for $C_{19}H_{26}NO_3$ (M^+ + 1) 316.1913, found 316.1905; $[\alpha]_D^{26}$ -33.2° (c 0.73, $CHCl_3$).

(*1S,5R,Z*)-5-(6-Hydroxy-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one ((*Z*)-19): To a solution of **18** (32 mg, 0.089 mmol) in acetonitrile/water (9/1) (0.32 mL) was added cerium ammonium nitrate (97 mg, 0.18 mmol) and the mixture was stirred for 15 min at rt. CH_2Cl_2 (8 mL) was added and the mixture was washed with saturated $NaHCO_3$ aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a yellow oil (27.6 mg). Column chromatography (34% EtOAc/hexane then EtOAc) gave 17.2 mg (82%) of **(*Z*)-19** as a colorless oil. ^1H NMR ($CDCl_3$) δ: 1.60-1.90 (m, 11H), 2.15 (dt, *J* = 7.3, 14.8 Hz, 2H), 4.19 (d, *J* = 6.8 Hz, 2H), 4.59 (d, *J* = 5.5 Hz, 1H), 5.49 (m, 1H, D_2O exchangeable), 5.50-5.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 23.01, 24.39, 27.18, 33.82, 38.58, 39.04, 58.13, 68.40, 86.59, 129.40, 131.63, 160.00; IR

(neat) 3290, 1731 cm^{-1}; MS (EI) m/z: 225 (M^+); HRMS calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1343; $[\alpha]_D^{26}$ -39.6° (c 1.66, $CHCl_3$).

(*1S,5R,E*)-5-(6-Hydroxy-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one (*(E)*-19): To a solution of **20** (209 mg, 0.66 mmol) in NH_3 (l) (6 mL) was added Li (12 mg, 0,096 mmol) at –78 ˚C. After 30 min, saturated NH_4Cl aq was added. The mixture was extracted with EtOAc (6 x 30 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a colorless oil (150 mg). Column chromatography (50% EtOAc/hexane then EtOAc) gave 115.3 mg (77%) of **(*E*)-19** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.70-1.90 (m, 10H), 2.10 (m, 2H), 4.10 (d, *J* = 2.3 Hz, 2H), 4.60 (d, *J* = 5.5 Hz, 1H), 5.63 (m, 1H, D_2O exchangeable), 5.66 (m, 2H); ^{13}C NMR ($CDCl_3$) δ : 23.02, 23.83, 32.02, 33.89, 38.52, 39.18, 65.72, 68.32, 86.43, 129.96, 131.77, 159.77; IR (neat) 3280, 1739 cm^{-1}; MS (FAB) m/z: 226 (M^+); HRMS (FAB) calcd for $C_{12}H_{20}NO_3$ (M^+ + 1) 226.1443, found 226.1445; $[\alpha]_D^{26}$ -37.1° (c 0.97, $CHCl_3$).

(*3aS,6S,9aR*)-6-Ethenyl-4-oxa-5a-azaperhydrocyclopenta[*c*]inden-5-one (21).

Cyclization of (*Z*)-19 with Pd (II): To a solution of $PdCl_2(C_6H_5CN)_2$ (20 mg, 0.053 mmol) in THF (1.5 mL) was added a solution of **19**(81.8 mg, 0.336 mmol) in THF (2.5 mL) at 0 ˚C and the mixture was stirred for 2h. The resulting mixture was diluted with ether and filtered through celite. The filtrate was washed with 10% HCl aq (20 mL), saturated $NaHCO_3$ aq (20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a brown oil (36.8 mg). Column chromatography (10% then 30% EtOAc/hexane) gave 22.7 mg (62%) of **21** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.42 (m, 1H), 1.70-1.80 (m, 9H), 1.97 (m, 2H), 2.27 (m, 1H), 4.41 (d, *J* = 5.5 Hz, 1H), 4.60 (s, 1H), 5.20 (dd, *J* = 1.4, 10.9 Hz, 1H), 5.27 (dd, *J* = 1.4, 17.8 Hz, 1H), 5.91(ddd, *J* = 4.6, 10.9, 17.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.99, 23.24, 26.50, 33.26, 35.85, 37.38, 50.59, 67.74, 85.95, 115.83, 137.96, 157.26; IR (neat) 1740, 1638 cm^{-1}; MS (EI) m/z: 207 (M^+); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1272; $[\alpha]_D^{26}$ -101.4° (c 2.07, $CHCl_3$).

Cyclization of (*E*)-19 with Pd (II): To a solution of $PdCl_2(C_6H_5CN)_2$ (7 mg, 0.018 mmol) in THF (1 mL) was added a solution of **19** (11.1 mg, 0.049 mmol) in THF (0.3 mL) at 0 ˚C and the mixture was stirred for 5 h. The resulting mixture was diluted with ether and filtered through celite. The filtrate was washed with 10% HCl aq (20 mL), saturated $NaHCO_3$ aq (20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a brown oil (7.1 mg). Column chromatography (10% then 30% EtOAc/hexane) gave 4.3 mg (42%) of **21** as a colorless oil.

(*1S,5R,7S*)-*N*-Methyl-7-ethenyl-6-azaspiro[4.5]decan-1-ol picrate (22): To a suspension of $LiAlH_4$ (35 mg, 0.92 mmol) in THF (1.0 mL) was added a solution of **21** (95.6 mg, 0.46 mmol) in THF (1 mL) at 0 ˚C, and then the reaction mixture was stirred for 16 h at rt. To the mixture were added water (0.035 mL), 15% NaOH aq (0.035 mL), and water (0.105 mL) successively, and the resulting suspension

was dried over Na_2SO_4, filtered, and concentrated to give 97.5 mg of the crude mixture. Alumina column chromatography (hexane then EtOAc) gave 56.1 mg (62%) of amino alcohol. A solution of the amino alcohol in hexane (1 mL) was treated with picric acid at rt to afford yellow solid, which was recrystalized from ether-acetonitrile to give the picrate (**22**) as yellow prisms. mp 132.7-133.9 ˚C; Anal. Calcd for $C_{18}H_{24}N_4O$: C, 50.94; H, 5.70; N, 13.20; Found; C, 50.86; H, 5.64; N, 13.13.

Crystal data for 22: $C_{18}H_{23}O_8N_4$, M = 424.00, monoclinic, apace group $P2_1$, a = 8.133000 (0) Å, b = 11.444000 (0) Å, c = 21.360001 (0) Å, β = 95.188004 (0) ˚, *V* = 1979.900024 (0) Å^3, *Z* = 4, *Dx* = 1.530 Mg m^{-3}, Dm = 1.500 Mg m^{-3}, Mo Ka radiation (λ = 0.71073 Å), Cell parameters from 128 reflections, θ = 1-24.8˚, μ = 1.058 mm^{-1}, T = 298 K, Crystal habit: Cube, Crystal size 0.6 x 0.4 x 0.3 mm, Crystal color: yellow, Mac Science DIP2200 diffractometer, θ/2θ scans, no absorption correction, 3615 measured reflections, 3438 independent reflections, 2639 observed reflections, R = 0.062, wR = 0.054, S = 1.028, 2639 reflections, 636 parameters, Only coordinates of H atoms refined, [I > 2.00σ(I)] R_{int} = 0, θ_{max} = 24.80˚, h = 0→ 9, k = 0 → 13, l = -26 → 25, (Δ/σ)max = 0.4307, $\Delta\rho_{max}$ = 0.30 eÅ^{-3}, $\Delta\rho_{min}$ = -0.19 eÅ^{-3}, No extinction correction, Data collection: MXC (MAC Science), Cell refinement: MXC (MAC Science), Data reduction: *CRYSTAN*, Program used to solve structure: *CRYSTAN SIR* 92, Program used to refine structure: *CRYSTAN*, Molecular graphics: *CRYSTAN*, Software used to prepare material for publication: *CRYSTAN*.

(*1S,5R,Z*)-5-(6-Chloro-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one ((*Z*)-23): To a solution of (*Z*)-**19** (72.2 mg, 0.32 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (78.2 mg, 0.64 mmol) in CH_2Cl_2 (7 mL) was added mesyl chloride (0.05 mL, 0.64 mmol) at 0 ˚C and the mixture was stirred for 4 h at rt. The reaction was diluted with CH_2Cl_2 (10 mL), washed with 5% HCl aq, saturated $NaHCO_3$ aq, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a colorless oil (111.7 mg). Column chromatography (30% EtOAc/hexane) gave 72.2 mg (92%) of (*Z*)-**23** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.60-1.90 (m, 10H), 2.18 (dt, *J* = 6.8, 14.9 Hz, 2H), 4.07 (d, *J* = 7.7 Hz, 2H), 4.60 (d, *J* = 5.5 Hz, 1H), 5.05 (m, 1H, D_2O exchangeable), 5.61 (dt, *J* = 7.7, 10.9 Hz, 1H), 5.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.98, 23.88, 26.88, 33.81, 38.69, 38.98, 39.20, 68.26, 86.48, 125.86,134.36,159.96; IR (neat) 3267, 1745 cm^{-1}; MS (EI) m/z: 243(M^+), 245 (M^+ + 2), 208 (M^+ - Cl); HRMS calcd for $C_{12}H_{18}NO_2Cl$ (M^+) 243.1026, found 243.1042; [α] $_D^{23}$ -35.0° (c 2.12, $CHCl_3$).

(*1S,5R,E*)-5-(6-Chloro-4-hexenyl)-2-oxa-4-azabicyclo[2.2.0]octan-3-one ((*E*)-23): To a solution of (*E*)-**19** (59.3 mg, 0.26 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (64.3 mg, 0.53 mmol) in CH_2Cl_2 (6 mL) was added mesyl chloride (0.04 mL, 0.53 mmol) at 0 ˚C and the mixture was stirred for 13.5 h at rt. The reaction was diluted with CH_2Cl_2 (10 mL), washed with 5% HCl aq, saturated $NaHCO_3$ aq, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a colorless oil (74.6 mg). Column chromatography (40% EtOAc/hexane) gave 60.3 mg (94%) of (*E*)-**23** as a colorless oil. ^{1}H NMR ($CDCl_3$)

δ: 1.60-1.90 (m, 10H), 2.11 (dt, *J* = 6.8, 13.7 Hz, 2H), 4.04 (d, *J* = 6.8 Hz, 2H), 4.60 (d, *J* = 5.5 Hz, 1H), 5.10 (m, 1H, D_2O exchangeable), 5.60 (dt, *J* = 6.8, 15.0 Hz, 1H), 5.80 (dt, *J* = 6.4, 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.02, 23.59, 31.94, 33.86, 38.71, 39.06, 45.14, 68.26, 86.50, 126.76, 134.87, 159.81; IR (neat) 3265, 1745, 1665 cm^{-1}; MS (EI) m/z: 243 (M^+), 245 (M^+ + 2), 208 (M^+ - Cl); HRMS calcd for $C_{12}H_{18}NO_2Cl$ 243.1026, found 243.1010; $[\alpha]_D^{23}$ -38.6° (c 1.50, $CHCl_3$).

Cyclization of 23 with Pd (0). General procedure: To a suspension of NaH (62.5% in mineral oil, 9 mg, 0.18 mmol) in THF (1 mL) was added a solution of **23** (30 mg, 0.12 mmol) in THF (1 mL) at 0 ˚C. To the mixture was added Pd (0) solution, prepared from $(PhC_2H_2COC_2H_2Ph)_3Pd_2$•$CHCl_3$ (12.7 mg, 0.012 mmol) and Ph_3P (25.8 mg, 0.098 mmol) in THF (1.4 mL) at rt, and the reaction mixture was stirred for 4 h at rt. After addition of saturated NH_4Cl aq, the mixture was extracted with ether and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give an orange oil (58.7 mg), which was purified with column chromatography (20% EtOAc/hexane then EtOAc) to afford **24** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.61-1.80 (m, 7H), 2.00-2.43 (m, 4H), 2.42 (m, 1H), 3.48 (d, *J* = 17.3 Hz, 1H), 4.40 (d, *J* = 17.8 Hz, 1H), 4.62 (d, *J* = 5.0 Hz, 1H), 5.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 22.50, 23.08, 23.50, 31.98, 34.06, 36.79, 41.05, 72.10, 81.57, 127.15, 127.77, 157.29; IR (neat) 1732 cm^{-1}; MS (EI) m/z: 207 (M^+); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1272; $[\alpha]_D^{26}$ -51.5° (c 1.58, $CHCl_3$).

(*3aS,6R,9aR*)-6-(2-Hydroxyethyl)-4-oxa-5a-azaperhydrocyclopenta[*c*]inden-5-one (25) and (*3aS,6S,9aR*)-6-(2-Hydroxyethyl)-4-oxa-5a-azaperhydrocyclopenta[*c*]inden-5-one (26): To a solution of a mixture (9.1 mg, 0.044 mmol) of diastereomers (**3**) and (**21**) in THF (0.3 mL) as added BH_3•SMe_2 (0.0036 mL, 0.034 mmol) dropwise at 0 ˚C, and the reaction mixture was stirred for 0.5 h at 0 ˚C and for 2 h at rt. To the resulting mixture were added water (0.15 mL), 2N NaOH (0.03 mL, 0.059 mmol), and 35% H_2O_2 (0.006 mL) at 0 ˚C, and the mixture was stirred for 1.5 h at 0 ˚C and for 1 h at rt. The reaction mixture was extracted with CH_2Cl_2 (4 x 10 mL), and the organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated to give a colorless oil (30.3 mg). Column chromatography (30% EtOAc/hexane) gave 7.1 mg of a mixture of **25** and **26**, which was purified with PTLC (33% EtOAc/CH_2Cl_2) to give **25** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.60-2.10 (m, 14H), 3.56 (dt, *J* = 2.7, 11.4 Hz, 1H), 3.68 (ddd, *J* = 2.7, 5.2, 12.4 Hz, 1H), 4.22 (ddd, *J* = 4.6, 6.8, 12.8 Hz, 1H), 4.50 (d, *J* = 5.01 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.81, 23.71, 29.68, 32.64, 35.88, 36.05, 38.52, 46.02, 58.78, 67.22, 87.48, 163.16; IR (neat) 3437, 1715 cm^{-1}; MS (EI) m/z: 225 (M^+), 180 (M^+ - CH_2CH_2OH); HRMS calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1367; $[\alpha]_D^{26}$ -10.7° (c 0.14, $CHCl_3$).

(*3aS,6S,9aR*)-6-(2-Hydroxyethyl)-4-oxa-5a-azaperhydrocyclopenta[*c*]inden-5-one (26): To a solution of **21** (20.6 mg, 0.099 mmol) in THF (0.7 mL) was added BH_3•SMe_2 (0.0082 mL, 0.078 mmol) dropwise at 0 ˚C, and the reaction mixture was stirred for 3 h at rt. To the resulting mixture were

added water (0.34 mL), 2N NaOH (0.07 mL), and 35% H_2O_2 (0.013 mL) at 0 ˚C, and the mixture was stirred for 2 h at rt. The reaction mixture was extracted with CH_2Cl_2 (4 x 10 mL), and the organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated to give a white oil (22.4 mg). Column chromatography (30% then 50% EtOAc/hexane), followed by further purification with column chromatography (ether), gave 3.9 mg of a mixture of **26** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.60-2.10 (m, 14H), 2.79 (dt, *J* = 5.0, 16.9 Hz, 1H), 3.37 (dt, *J* = 2.7, 4.3 Hz, 1H), 3.77 (ddd, *J* = 6.4, 6.8, 10.6 Hz, 2H), 4.36 (dd, *J* = 2.3, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.91, 23.37, 32.39, 33.38, 34.23, 34.37, 35.18, 51.86, 60.68, 70.35, 84.32, 165.70; IR (neat) 3418, 1715 cm^{-1}; MS (EI) m/z: 225 (M^+); HRMS calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1376; $[\alpha]_D^{26}$ -60.3° (c 0.58, $CHCl_3$).

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12. When the reaction was conducted without Pd(0) catalyst, the tricycle (**24**) was obtained in 70% yield. This result suggests that the reaction shown in entry 3 (in Table 1) may be S_N2 type cyclization without intervention of π-allyl palladium complex.
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