Highly Stereoselective Total Syntheses of (+)-Allopumiliotoxins 267A and 339A via Intramolecular Nickel(II)/Chromium(II)-Mediated Cyclization

Sakae Aoyagi, Tzu-Chueh Wang, and Chihiro Kibayashi*

Contribution from the Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

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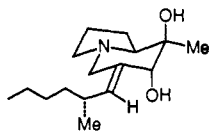
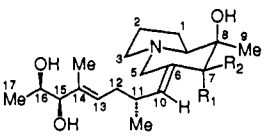
Abstract: Remarkably high regio- and stereoselective approaches for the syntheses of dendrobatid alkaloids (+)-allopumiliotoxin 267A and 339A have been developed. As a model study for the syntheses of these alkaloids, we initially undertook intramolecular chromium(II)-mediated cyclization of the racemic *N*-(iodoalkenyl)piperidine **8**, which smoothly proceeded by treatment with $CrCl_2$ (5 equiv) and catalytic $NiCl_2$ (2.5 mol %) in DMF to form a 1.3:1 epimeric mixture of 2-hydroxy-3(*E*)-alkylidene-*trans*-quinolizidines **33a** and **33b**. When the alternative chiral *N*-(iodoalkenyl)piperidine **9** was subjected to the identical cyclization conditions, the 3(*E*)-alkylidene-*trans*-quinolizidine **35a** with the axially oriented 2-hydroxy group was formed as a single isomer. Based on these model studies, we then undertook the enantioselective total synthesis of (+)-allopumiliotoxin 267A (**1**). For the synthesis of (+)-allopumiliotoxin 267A (**1**), coupling of the two segments, (*E*)-vinyl iodide **45**, obtained via stereospecific palladium-catalyzed hydrostannation, and the pyrrolidine derivative **54**, gave the *N*-(iodoalkenyl)pyrrolidine **56**, which underwent intramolecular chromium-(II)-mediated cyclization, exclusively providing **58** with complete retention of the required (*E*)-alkenyl geometry. Subsequent cleavage of the benzyl group furnished **1**. Synthesis of allopumiliotoxin 339A (**2**) was next investigated by employing the strategy developed for **1**. The side-chain segment, (*E*)-vinyl iodide **74**, was prepared via high-degree stereo- and regioselective reactions involving Evans alkylation and palladium-catalyzed hydrostannation. Intramolecular nickel(II)/chromium(II)-mediated cyclization of the *N*-(iodoalkenyl)pyrrolidine **82**, available via coupling **74** with pyrrolidine derivative **79**, led to exclusive formation of **83**, which was deprotected to afford **2**.

Neotropical poison-dart frogs of the family Dendrobatidae have been a rich source of various structurally unique and biologically significant alkaloids.[1] Virtually all of these alkaloids possess high pharmacological activity on nerve and muscle. After the early discovery of four classes of dendrobatid alkaloids that are of the pumiliotoxin C class, the histrionicotoxins, gephyrotoxins, and batrachotoxins, new members of the pumiliotoxin A class and their allo series were isolated and structurally defined.[2] The latter subclass of alkaloids, the allopumiliotoxins, is a group of hydroxy congeners of the pumiliotoxin A class which possess the characteristic structural features of vicinal dihydroxy groups at C-7 and C-8 in the indolizidine ring and a 6-alkylidene side chain bearing (*E*) configuration. The challenging structure of these alkaloids and the intriguing pharmacological activities as well as the extreme scarcity of the natural products have combined to motivate development of organic synthesis. To date, two groups in addition to our own have reported total syntheses of allopumiliotoxins. The pioneering work by Overman and co-workers[3] on total syntheses of allopumiliotoxins 267A (**1**) and 339B (**3**) constitutes the first synthetic breakthrough in this area. Subsequently, the significant accomplishment of a synthesis of allopumiliotoxin 339B was reported by Trost's group.[4] More recently, the first total synthesis of allopumiliotoxin 339A (**2**), which is the most biologically active of the allopumiliotoxin family, was published by Overman's group.[5] From the structural point



(+)-Allopumiliotoxin 267A (1)



(+)-Allopumiliotoxin 339A (2, R_1 = OH; R_2 = H)

(+)-Allopumiliotoxin 339B (3, R_1 = H; R_2 = OH)

of view, the two allopumiliotoxin alkaloids **2** and **3**, which differ only in the configuration at C-7, may be considered the most complex representatives of the indolizidine class of naturally occurring alkaloids.[6] The most conspicuous feature common to allopumiliotoxins 267A (**1**) and 339A (**2**)[7] which sharply defines them from allopumiliotoxin 339B (**3**) is the presence of the axially oriented 7-hydroxy group in the indolizidine nucleus. In addition to this structural characteristic, the unique structural feature of the 6(*E*)-alkylideneindolizidine system clearly poses a significant challenge for **1** and **2**. Preparation of stereodefined exocyclic

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(7) Isolation and structure elucidation of allopumiliotoxins 267A (**1**) and 339A (**2**) were originally reported by Daly et al. in ref 2b, in which the relative configurations of **1** and **2** were represented as 7*R**,8*R**,11*S** and 7*R**,8*R**,-11*S**,15*S**,16*S**, respectively, with the configuration of 8a-C unidentified. However, Overman's group has recently designated the stereostructures and absolute configurations of these alkaloids as 7*R*,8*R*,8a*S*,11*R* and 7*R*,8*R*,-8a*S*,11*R*,15*R*,16*R*, respectively, as depicted in structures **1** and **2**, by means of total syntheses of these alkaloids (refs 3 and 5). Our syntheses of **1** and **2** were based on these stereostructures defined by Overman's group.

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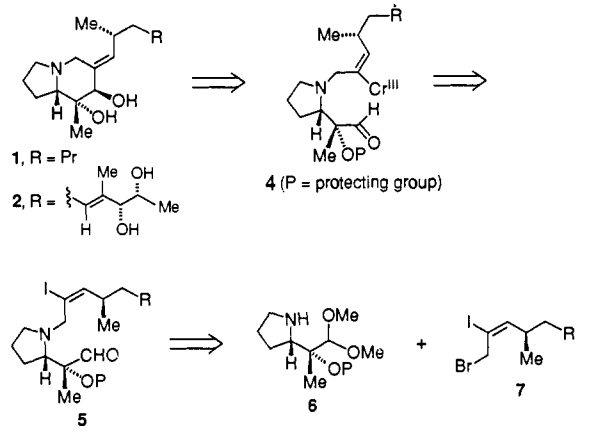
Scheme I

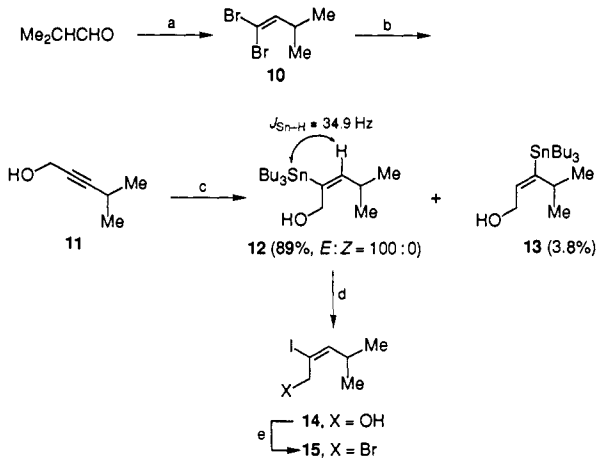


(*E*)-alkenes seems an important objective for development,[8] since various types of natural and nonnatural products, including the pumiliotoxin A class,[9] containing exocyclic alkenyl moieties have been shown to possess significant biological and medicinal activities. In this paper we present a full account of our efforts toward highly regio- and stereocontrolled total syntheses of (+)-allopumiliotoxins 267A (**1**) and 339A (**2**).[10]

Results and Discussion

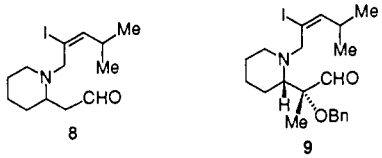
Synthetic Strategy. Our general approach to synthesis of both (+)-allopumiliotoxins 267A (**1**) and 339A (**2**) is outlined in retrosynthetic format in Scheme I. We intended to establish the 6(*E*)-alkylideneindolizidine framework carrying the trans diaxial 7,8-dihydroxy function in the last step. For this critical step we envisioned an intramolecular approach based on alkenyl metal cyclization involving a chromium-mediated coupling reaction[11] taking place via the vinylchromium intermediate **4** (for **2**, with the hydroxy groups in the side chain adequately protected). Such reaction involving carbon–carbon bond formation between vinylchromium compounds and aldehydes was first described by Nozaki and co-workers.[12] A great portion of the investigation involving vinylchromium reagents was subsequently carried out by Kishi and co-workers.[13] The *N*-(iodoalkenyl) aldehydes **5** required for this cyclization in the retrosynthetic sequence should be readily available by coupling of the pyrrolidine fragment **6** and the geometrically and stereochemically defined (*E*)-vinyl iodides **7**. These disconnections would give us the flexibility required to synthesize these allopumiliotoxins with different side chains.

Scheme II[a]



[a] (a) CBr_4, PPh_3, CH_2Cl_2, room temperature (82%); (b) $(CH_2O)_n$, BuLi (2 equiv)/hexane, THF, −78 °C to room temperature (81%); (c) Bu_3SnH (1.1 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), CH_2Cl_2, room temperature; (d) I_2, CH_2Cl_2, −78 °C to room temperature (95%); (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C (96%).

Preliminary Model Studies of Chromium(II)-Mediated Cyclization. With this highly convergent route in mind, our initial efforts focused on testing the feasibility of chromium-mediated cyclization[14] for direct construction of the (*E*)-alkylidenepiperidine system with the axial hydroxy group on the piperidine ring in a single step using model compounds. To this end, we chose to model our key cyclization with the piperidines **8** and **9** both bearing a common (*E*)-iodoalkenyl moiety. We therefore initially



elaborated the (*E*)-iodoalkenyl segment as outlined in Scheme II. Isobutyraldehyde was converted to the dibromide **10** in 82% yield by treatment with CBr_4 and PPh_3.[15] Upon exposure to 2 equiv of butyllithium in THF followed by paraformaldehyde, **10** was transformed into 4-methyl-2-pentyn-1-ol (**11**) in 81% yield. In an effort to generate the required (*E*)-olefin geometry, we envisioned utilizing the palladium-catalyzed hydrostannation of alkynes.[16] This strategy promised, in effect, to introduce the (*E*)-alkenylstannane **12** required for the subsequent formation of the (*E*)-vinyl iodide **14** by iododestannation. Indeed, when the propargyl alcohol **11** was allowed to react with 1.1 equiv of tributyltin hydride in the presence of catalytic $PdCl_2(PPh_3)_2$ (2 mol %), the 2-(tributylstannyl)alkene **12** (89% yield) was produced along with a minor amount of the 3-tributylstannyl isomer **13** (3.8%), both of which were readily separable by column chromatography. The (*E*) geometry of **12** was verified by the ^1H NMR spectrum, which shows a small coupling constant of 34.9 Hz[17] between the Sn and the olefinic proton at C-3 (Scheme II).

As was expected, this palladium-catalyzed hydrostannation reaction following syn addition led to the (*E*)-vinyltin **12** in a stereospecific manner. This is noteworthy because hydrostan-

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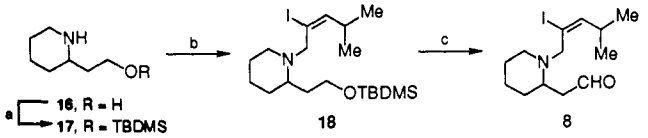
Scheme III[a]



[a] (a) (i) CbzCl, aqueous Na_2CO_3, CH_2Cl_2, room temperature (87%); (ii) *t*-$BuMe_2SiCl$, imidazole, DMAP, DMF, room temperature (99%); (iii) H_2, 10% Pd–C, MeOH (95%); (b) **15**, *i*-Pr_2NEt, THF, room temperature (84%); (c) (i) Bu_4NF, THF, room temperature (81%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (86%).

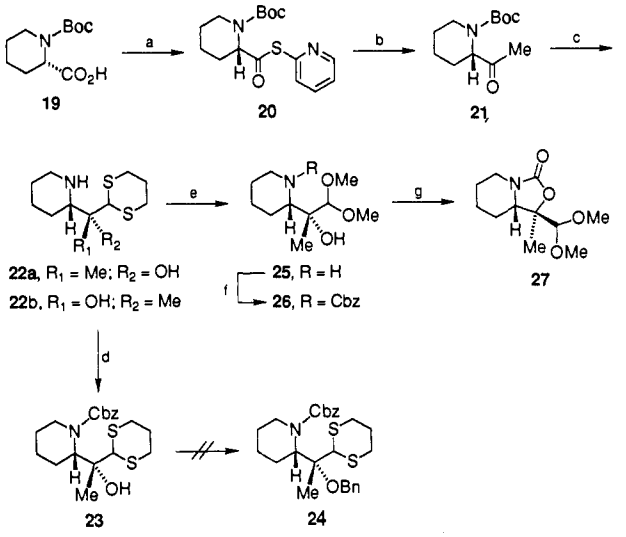
nation of nonterminal alkynes under free-radical conditions is known to follow trans addition, leading to (*Z*)-isomers as primary adducts.[18] Unlike the stereoselectivity, the regioselectivity of this free radiacal reaction is not necessarily high—usually modest to low. In the present case involving palladium-catalyzed hydrostannation, while the rationale for the regiochemistry of hydrostannation is not clear-cut, the high degree of regioselection (96:4) presumably results from the steric effect of the isopropyl group and coordinate interaction between the carbinol oxygen atom and the tin.

Upon exposure of **12** to iodine, iododestannation[19] proceeded with complete retention of the (*E*)-olefin geometry to form the stereochemically defined (*E*)-vinyl iodide **14** in excellent yield (95%). Subsequent bromination of **14** with CBr_4 and PPh_3 furnished **15** in 96% yield.

As illustrated in Scheme III, the first cyclization substrate **8** required for preliminary investigation was prepared starting from commercially available racemic 2-piperidineethanol (**16**), which was readily converted to the O-protected racemic piperidineethanol **17** in three steps by standard method involving Cbz N-protection, silyl protection of the primary alcohol, and hydrogenolytic removal of the Cbz protecting group. Coupling of the iodoalkenyl segment **15** with the piperidine **17** conducted in the presence of Hünig's base (1.5 equiv) in THF yielded **18** (84%), which was subjected to desilylation followed by Swern oxidation[20] to give the objective (*E*)-iodoalkenyl aldehyde **8** in 70% overall yield.

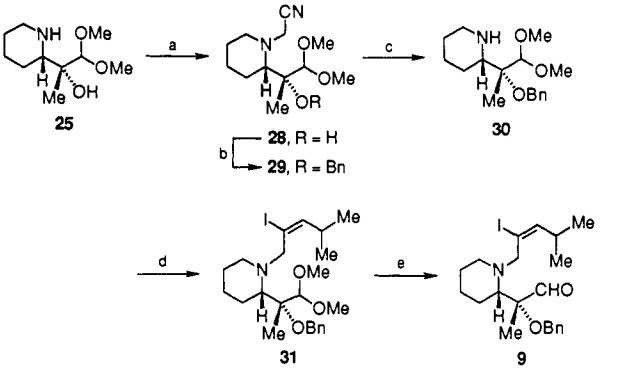
We next focused our efforts on the preparation of the alternative cyclization substrate **9** starting with *N*-Boc-L-pipecolinic acid (**19**).[21] Thus, Mukaiyama methodologies[22,23] were successfully applied to incorporate the acetyl moiety by treatment of **19** with 2,2′-dipyridyl disulfide and PPh_3 affording the thiolester **20** (94% yield), which underwent Grignard reaction with MeMgBr (THF, 0 °C) to give the methyl ketone **21** (72% yield) as outlined in Scheme IV. Deprotection of the *N*-Boc group in **21** by exposure to trifluoroacetic acid (3 equiv) at room temperature led to the formation of the piperidine trifluoroacetate salt, which was (without purification) immediately treated with excess 2-lithio-1,3-dithiane[24] in THF at −50 °C; this treatment generated the tertiary alcohols **22a** and **22b** in 72% combined yield with 6.2:1 diastereoselectivity as predicted by Cram's model[25] based on participation of the piperidine nitrogen atom, giving a rigid cyclic complex with the lithium compound.[26] Recrystallization of this mixture from ether gave the diastereomerically pure alcohol **22a**.

Scheme IV[a]



[a] (a) PySSPy, PPh_3, MeCN, reflux (94%); (b) MeMgBr, THF, 0 °C (72%); (c) CF_3CO_2H (3 equiv), CH_2Cl_2, room temperature, and then 1,3-dithiane (6 equiv), BuLi (6 equiv)/hexane, THF, −78 °C to −50 °C (72%, **22a**:**22b** = 6.2:1); (d) CbzCl, aqueous K_2CO_3, CH_2Cl_2, room temperature (88%); (e) $Hg(ClO_4)_2 \cdot 3H_2O$, MeOH–$CHCl_3$, room temperature (76%); (f) CbzCl, aqueous K_2CO_3, CH_2Cl_2, room temperature (92%); (g) BnBr, KH, THF, room temperature (95%).

Scheme V[a]



[a] (a) ICH_2CN, *i*-Pr_2NEt, THF, room temperature (83%); (b) BnBr, KH, THF, room temperature (92%); (c) $AgNO_3$, EtOH, room temperature (93%); (d) **15**, *i*-Pr_2NEt, DMF, room temperature (72%); (e) BCl_3, CH_2Cl_2, −78 °C, and then aqueous $NaHCO_3$ (62%).

After Cbz N-protection, the resulting carbamate **23** was treated with benzyl bromide under basic conditions (*t*-BuOK or KH) in an attempt at benzylation of the tertiary alcohol group to produce **24**. However, this resulted only in low yield of an unidentified product isolated from a complex mixture. In this case, the cyclic dithioacetal was considered to be inadequate as the aldehyde protecting group owing to its bulkiness and lability under the basic conditions. In view of these factors, we thus envisioned changing the aldehyde protecting group from the cyclic dithioacetal to the corresponding dimethyl acetal. Accordingly, the transformation of the cyclic dithioacetal **22a** into the dimethyl acetal **25** was achieved by treatment with $Hg(ClO_4)_2$ in methanol–$CHCl_3$ in 76% yield. After Cbz N-protection, an attempt at O-benzylation of **26** using the identical conditions led only to the formation of the cyclic carbamate **27**.

To counter this problem, we decided to incorporate the cyanomethyl group[27] instead of the Cbz group as an N-protecting group (Scheme V). Thus, blocking of the amino group by the cyanomethyl group provided **28** (83% yield), and O-benzylation was successfully achieved by treating this compound with benzyl

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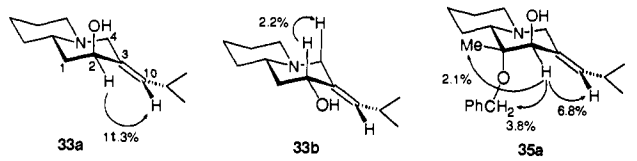
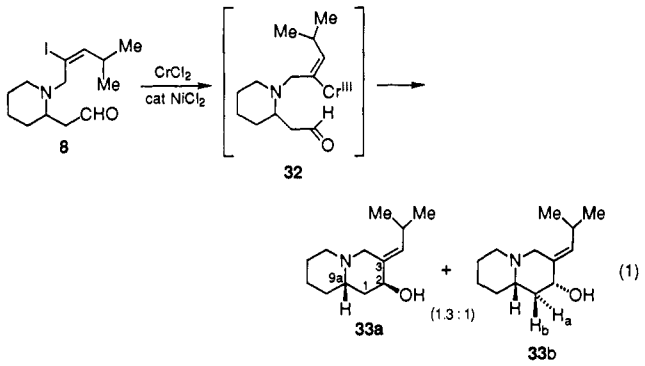


Figure 1. Selected NOE enhancements of **33a**, **33b**, and **35a**.

bromide and KH at room temperature, producing **29** in 92% yield. Deblocking of the cyanomethyl group with $AgNO_3$[27] followed by application of the above coupling conditions to **30** led to **31**, which was converted to the alkenyl aldehyde **9** by acetal deblocking with BCl_3 followed by aqueous workup.

With the (*E*)-iodoalkenyl aldehydes **8** and **9** thus in hand, nickel(II)/chromium(II)-mediated cyclization was performed as follows. Treatment of **8** with 5 equiv of chromium(II) chloride in the presence of a catalytic amount of nickel(II) chloride (2.5 mol %) in DMF at room temperature resulted in the direct construction of the 2-hydroxy-3(*E*)-alkylidene-*trans*-quinolizidine system, thus affording a trans/cis (with respect to C-2 and C-9a) mixture of **33a** and **33b** in 81% combined yield, thereby providing a slight diastereomeric bias for trans selectivity of 1.3:1 (eq 1).



The presence of moderately strong bands in the Bohlmann region in the IR spectrum (see Experimental Section) of the products indicated that these substances possessed a trans ring fusion. The stereochemical assignments of both diastereomers **33a** and **33b** were determined by NOE measurements, two of the most informative of which are illustrated in Figure 1. On irradiation of the C-2 proton in the trans diastereomer **33a**, a marked NOE enhancement (11.3%) of the C-10 olefinic proton occurred, indicating the equatorial 2-H and the (*E*)-alkylidene geometry. In the case of the cis diastereomer **33b**, enhancement between the C-2 and C-4 protons (on irradiation of the C-2 proton) was indicative of a cis diaxial relationship of these protons. The equatorial hydroxy group in **33b** was supported by ^{1}H NMR analysis; in the ^{1}H NMR spectrum of **33b** we have observed the coupling constants of vicinal 2-H/1-H_a and 2-H/1-H_b at 10.4 and 3.7 Hz, respectively, the former of which confirms a trans diaxial relationship between the corresponding protons (2-H and 1-H_a), thus proving that the hydroxy group at C-2 is in the equatorial position, in accord with the assigned structure for **33b**.

This cyclization would proceed via initial oxidative addition of the alkenyl iodide to Ni(0) to provide a Ni(II) species and then transmetalation with Cr(III) to form the alkenylchromium(III) intermediate **32** (eq 1), which leads to the alkylidenequinolizidine ring with complete retention of the (*E*)-alkene geometry. Ni(0) and Cr(III) are generated by the facile redox coupling between Ni(II) and Cr(II); during the cyclization process, Ni(II) is regenerated and recycled. The trans preference providing **33a** is predicted by the chairlike transition-state conformer **8A**, with the chromium(III) alkoxide group adopting an axial orientation (Figure 2) in which an allylic 1,3-strainlike interaction[28] between

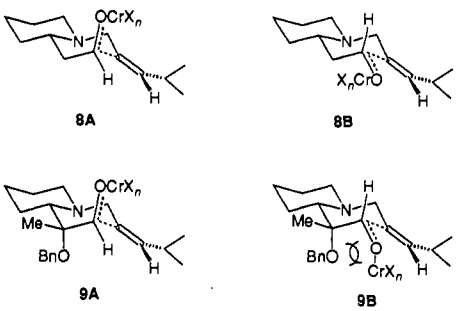
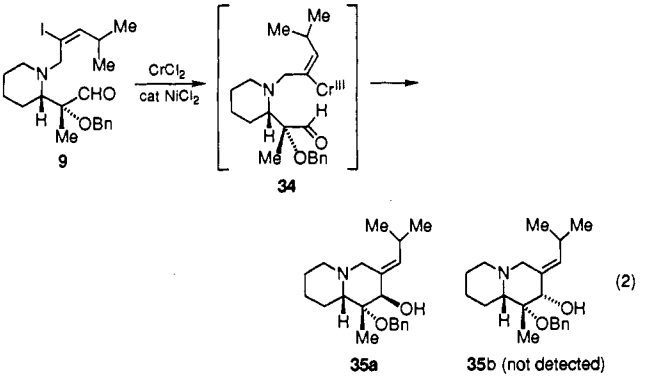


Figure 2.

the chromium(III) alkoxide and the olefin (as depicted by **8B** in Figure 2) is avoided. However, this cyclization process, at least in this simple model, displayed a much lower level of selectivity, thus suggesting that the allylic 1,3-strain may contribute little to the emergence of the trans selectivity.

In marked contrast to this, a dramatic increase in selectivity was observed when the iodoalkenyl aldehyde **9** was subjected to the nickel(II)/chromium(II)-mediated cyclization conditions (eq 2) as above. This cyclization resulted in the formation of the

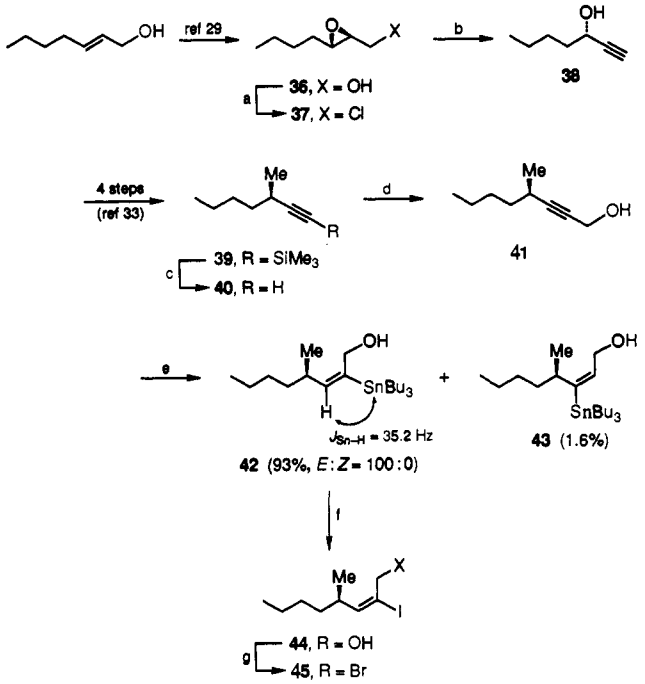


trans-quinolizidine **35a** in 53% yield with no evidence of the formation of the C-2 epimer **35b** detected in the 400-MHz ^{1}H NMR spectrum. The anti arrangement at C-1 and C-2 as well as the (*E*)-alkylidene geometry in **35a** was based on NOE enhancements in the ^{1}H NMR spectrum, the results of which are summarized in structure **35a** in Figure 1. On irradiation of the C-2 proton, NOEs were observed on the C-1 methyl proton, the benzylic methylene proton, and the C-10 olefinic proton, confirming that the C-2 proton is oriented in equatorial position. A strong intensity enhancement (6.8%) in the C-10 olefinic proton clearly proved that the 3,10-exo double bond was in the (*E*) configuration. This extremely high induction of the axial 2-hydroxy group in the cyclization of **9** could not be fully rationalized by avoidance of the allylic 1,3-strain between the chromium(III) alkoxide and the olefin present in the chairlike conformer **9B** (leading to **35b** with the 2-equatorial hydroxy group), because, as discussed above, the allylic 1,3-strain would not be the major control element for the axial selectivity. However, the conformer **9B** is much more severely destabilized by steric hindrance/electrostatic repulsion between the vicinal oxygen functional groups at C-1 and C-2 (by quinolizidine numbering), adopting a quasiaxial and quasiequatorial positions, respectively. The alternative chairlike conformer **9A**, leading to **35a** with the axial 2-hydroxy group, is quite free from these interactions and, as a consequence, must be strongly favored over the conformer **9B**.

A highly efficient methodology for constructing the bicyclic framework with the exocyclic (*E*)-alkene and the trans diaxial diol moieties in a single operation via intramolecular nickel(II)/chromium(II)-mediated cyclization was thus established. It should be emphasized that in this cyclization the oxygen

(28) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

Scheme VI[a]



[a] (a) Ph_3P, CCl_4, reflux (92%); (b) BuLi/hexane, THF, −35 °C (91%); (c) Bu_4NF, THF, room temperature (87%); (d) $(HCHO)_n$, BuLi/hexane, THF, −78 °C to room temperature (85%); (e) Bu_3SnH (1.1 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), THF; (f) I_2, CH_2Cl_2, 0 °C to room temperature (98%); (g) CBr_4, PPh_3, CH_2Cl_2, 0 °C (99%).

functionality (i.e., benzyloxy group) at the tertiary carbon atom in the cyclization substrate plays a crucial role in creation of the axial hydroxy group. With the model reaction satisfyingly thus in hand, the stage was set for the total synthesis of allopumiliotoxins 267A and 339A.

Total Synthesis of (+)-Allopumiliotoxin 267A. We initially targeted application of the foregoing retrosynthetic plan and the model approach to the total synthesis of allopumiliotoxin 267A (**1**). To this end, our first efforts were directed toward elaboration of the alkene side-chain segment, (*E*)-allyl bromide **45**, as outlined in Scheme VI. Asymmetric epoxidation[29] of commercially available 2-hexenol using diethyl L-tartrate gave **36**,[30] which was converted to (*S*)-1-heptyn-3-ol (**38**) under the conditions developed in Takano's laboratory.[31] Chlorination of the epoxy alcohol **36** with CCl_4 and PPh_3 followed by treatment with butyllithium (3 equiv) provided **38** in 84% overall yield. A 94% ee of this compound was determined from the 400-MHz ^1H NMR spectrum of its (*S*)-MTPA ester.[32] Following the use of Overman's method[33] in four steps, the (*R*)-silylalkyne **39** was then derived from the heptynol **38**. After desilylation (Bu_4NF), the resulting alkyne **40** underwent hydroxymethylation using paraformaldehyde and butyllithium, producing (*R*)-4-methyloctynol (**41**) in 74% overall yield from **39**. Construction of the requisite (*E*) geometry was successfully achieved by applying stereospecific syn addition to the propargyl alcohol utilizing palladium-catalyzed hydrostannation as established in the model study. Accordingly, when the propargyl alcohol **41** was treated with Bu_3SnH (1.1 equiv) in the presence of $PdCl_2(PPh_3)$ (2 mol %), a 98.3:1.7 mixture of the 2-(tributylstannyl)alkene **42** with correct (*E*)-olefin geometry ($J_{Sn-3,H}$ = 35.2 Hz) and its 3-tributylstannyl

(29) Hanson, R. M.; Sharpless, B. M. *J. Org. Chem.* **1986**, *51*, 1922. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

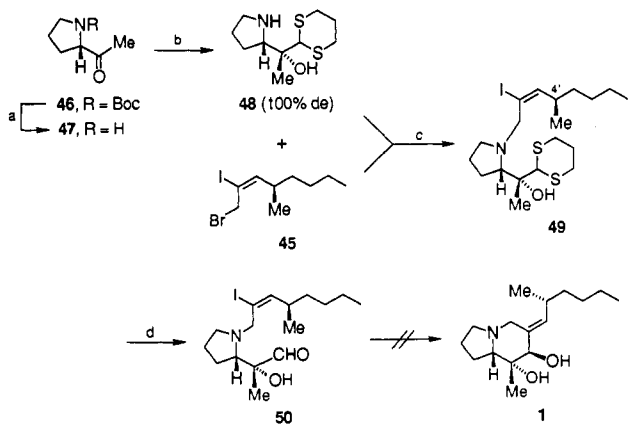
(30) Wang, Z. N.; Zhou, W. S. *Tetrahedron* **1987**, *43*, 2935.

(31) Takano, S.; Samizu, K.; Sugihara, K.; Ogasawara, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1344.

(32) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(33) Overman, L. E.; Kenneth, L. B.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

Scheme VII[a]



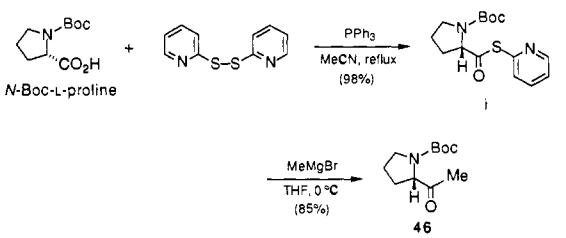
[a] (a) CF_3CO_2H (3 equiv), CH_2Cl_2, room temperature; (b) 1,3-dithiane (5 equiv); BuLi (5 equiv)/hexane, THF, −78 °C (54% from **46**); (c) *i*-Pr_2NEt, THF, room temperature (65%); (d) $Hg(ClO_4)_2 \cdot 3H_2O$, THF, room temperature (95%).

regioisomer **43** was produced; this mixture was readily separated by column chromatography to provide **42** in 93% yield. Iododestannation of **42** by treatment with iodine in CH_2Cl_2 gave the (*E*)-vinyl iodide **44**, with complete conservation of regio- and stereochemistry in excellent yield, which was shown to have an 84% ee by ^1H NMR analysis of the corresponding (*S*)-MTPA ester. Bromination of **44** with CBr_4 and PPh_3 in CH_2Cl_2 provided almost quantitatively the (*E*)-allyl bromide **45**.

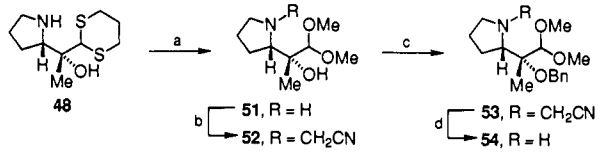
We next turned our attention to the preparation of the pyrrolidine function **48** (Scheme VII) based on the protocol sequence previously described for the preparation of **22a**. Deprotection of *N*-Boc-protected (*S*)-2-acetylpyrrolidine **46**,[3b,4] prepared from *N*-Boc-L-proline in two steps,[34] with trifluoroacetic acid (3 equiv) afforded the trifluoroacetate salt of **47**,[3,4] which was immediately treated with 2-lithio-1,3-dithiane (5 equiv) in THF at −78 °C to −50 °C to produce the tertiary alcohol **48** as a single diastereomer with generation of the desired chirality according to Cram's cyclic model, as described above in the model process **21** → **22a**. Coupling of **48** with the allyl bromide **45** (with 84% ee) in the presence of Hünig's base provided **49** in 65% yield. At this stage, the C-4′ isomer (4%), originated from a small contaminant of the (*S*)-enantiomer in the allyl bromide **45**, was separated by chromatography. Diastereomerically pure **49** thus obtained was subjected to dethioketalization with $Hg(ClO_4)_2$ to form the iodoalkenyl aldehyde **50** in 95% yield. In an attempt to synthesize allopumiliotoxin 267A (**1**), **50** was subjected to the chromium(II)-mediated conditions ($CrCl_2$ (5 equiv), $NiCl_2$ (2.5 mol %), DMF) developed in the preliminary cyclization study; however, only a complicated mixture of the products was formed, and the expected cyclization did not materialize.

Having been thwarted in this attempt at cyclization by way of the free-hydroxy-containing aldehyde **50**, we turned to use of a benzyl-protected substrate for the cyclization. To this end, introduction of the benzyl group was conducted as in the model experiments. Thus, as shown in Scheme VIII, the dithioketalized

(34) Preparation of **46** was carried out according to the model sequence **19** → **21** based on the thiol esterification–Grignard reaction protocol as follows:

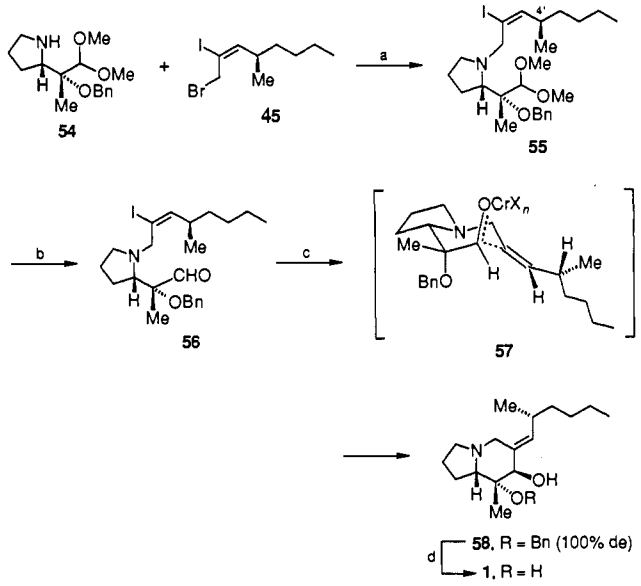


Scheme VIII[a]



[a] (a) $Hg(ClO_4)_2 \cdot 3H_2O$, MeOH–$CHCl_3$, room temperature (68%); (b) ICH_2CN, Et_3N, THF, room temperature (89%); (c) BnBr, KH, THF, reflux (91%); (d) $AgNO_3$, EtOH, room temperature (95%).

Scheme IX[a]



[a] (a) *i*-Pr_2NEt, THF, room temperature (69%); (b) me_2BBr, CH_2Cl_2, −78 °C, and then aqueous $NaHCO_3$ (67%); (c) method A, $CrCl_2$ (5 equiv), $NiCl_2$ (2.5 mol %), DMF, room temperature (53%); method B, $CrCl_2$ (5 equiv), $Ni(acac)_2$ (2.5 mol %), DMF, room temperature (31%); (d) Li, NH_3/THF, −78 °C (90%).

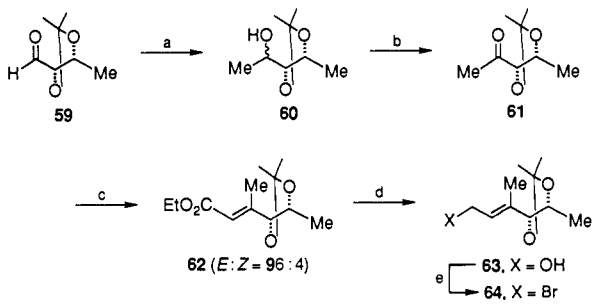
pyrrolidine **48** was allowed to react with methanol and $Hg(ClO_4)_2$ to give the dimethyl acetal **51** (68%). Subsequent protection of the amino group by the cyanomethyl group yielded **52** (89%), which smoothly underwent O-benzylation (benzyl bromide and KH in refluxing THF) to afford **53** in 91% yield. Deblocking of the cyanomethyl group with $AgNO_3$ in ethanol gave the desired pyrrolidine **54** in 95% yield.

Coupling of the two segments **54** and **45** (with 84% ee) in the presence of Hünig's base followed by chromatographic separation provided the diastereomerically pure *N*-iodoalkenylpyrrolidine **55**[35] in 69% yield, Scheme IX. The dimethyl acetal in **55** was then cleaved by treatment with Me_2BBr in THF at −78 °C, followed by aqueous workup, affording the (*E*)-iodoalkenyl aldehyde **56** (67%). Intramolecular cyclization of **56** was accomplished by applying the mild conditions ($CrCl_2$, catalytic $NiCl_2$, DMF, room temperature) developed in the preliminary cyclization study. The chromium-mediated coupling reaction thereupon proceeded through the alkenylchromium(III) intermediate (**4** in Scheme I), giving rise to **58** in 53% yield with no evidence of the C-7 epimer in the 400-MHz ^1H NMR spectrum. When this cyclization was performed using nickel acetylacetonate as a catalyst, the product (**58**) yield was only 31%. The cyclization occurred with complete retention of double-bond stereochemistry and with axial orientation of the resulting hydroxy group. As in the cyclization process **9** → **35a** (eq 2) in the model studies, the extremely high degree of diastereoselectivity in this process, **56** → **58**, can be explained by a chairlike transition state **57**, in which the benzyloxy and the chromium(III) alkoxide groups must be antiperiplanar to avoid an unfavorable allylic 1,3-strain between the quasiequatorial chromium alkoxide and the olefin and, more importantly, a steric/polar effect between the benzyloxy group and the chromium alkoxide groups bearing a partial negative charge. These interactions are matched in destabilizing the alternative equatorial predictable conformer (analogous to the transition conformer **9B** in Figure 2 mentioned above in the model study) and consequently effect excellent axial selectivity, albeit the allylic 1,3-strain would not be a critical element in the selectivity as discussed above in the model studies.

Completion of the synthesis of (+)-allopumiliotoxin 267A (**1**) was accomplished via reductive cleavage of the benzyl group of **58** by the dissolving metal protocol with lithium in ammonia (90% yield). The synthetic material of **1** ($[\alpha]^{25}_D$ +24.1 (*c* 1.1, MeOH)) was found to be identical with the natural product ($[\alpha]^{25}_D$ +24.7 (*c* 0.2, MeOH))[2b] in all respects (^1H and ^{13}C NMR, MS).

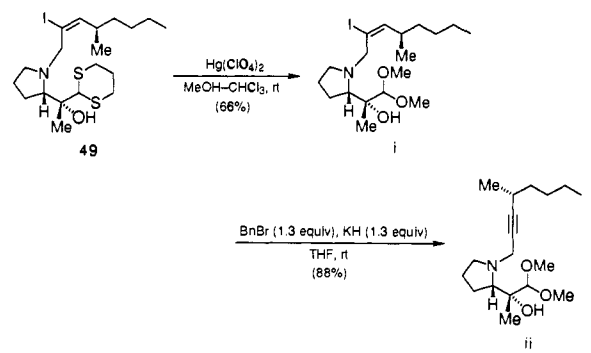
Total Synthesis of (+)-Allopumiliotoxin 339A. Having demonstrated the feasibility of the sequence for the approach to the allopumiliotoxin alkaloid, we further investigated extension of the above strategy to the preparation of allopumiliotoxin 339A (**2**). Toward this end, the sequence began with the elaboration of the side-chain segment (i.e., **74** depicted in Scheme XI). Thus, the known D-4-deoxythreose derivative **59**[36] was subjected to Grignard reaction (MeMgBr, THF) followed by PCC oxidation to provide the methyl ketone **61** (73% overall yield), which was transformed to the unsaturated ester **62** (84%) by Horner–Emmons condensation with a nice *E*/*Z* ratio of 96:4 (Scheme X). The (*E*)-ester **62** separated by column chromatography was sequentially treated with DIBALH and with CBr_4/PPh_3 to give the allyl bromide **64** in 91% yield. Evans protocol[37] seemed well suitable for subsequent creation of the *R* chiral center as well as C_2 homologation, leading to the (2*R*,6*R*,7*R*)-octenol **67**. In this

Scheme X[a]



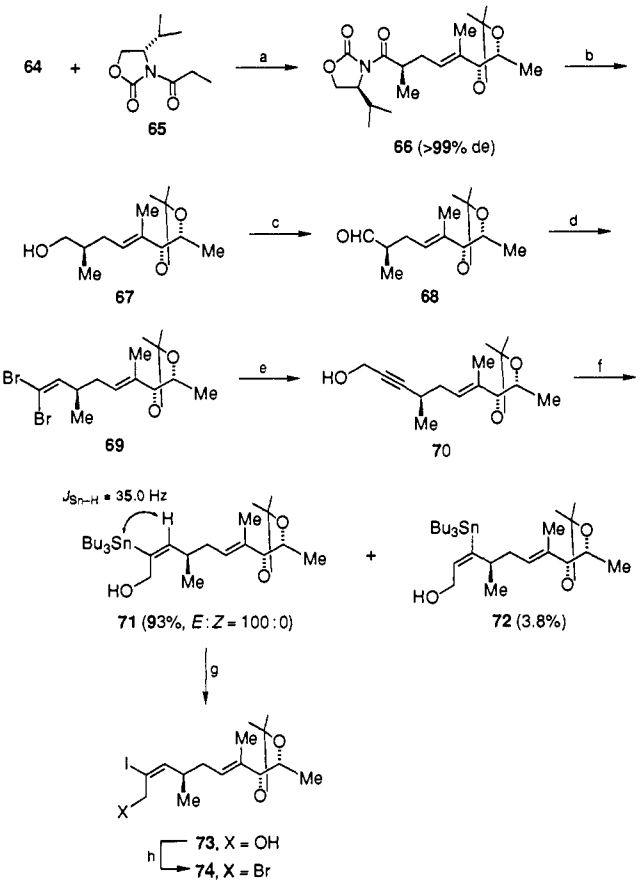
[a] (a) MeMgBr, THF, 0 °C (87%); (b) PCC, CH_2Cl_2, room temperature (84%); (c) $(i\text{-}PrO)_2POCH_2CO_2Et$, NaH, benzene, room temperature (84%); (d) DIBALH/hexane, CH_2Cl_2–hexane, −78 °C (97%); (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C (94%).

(35) In an anticipation of obtaining **55** from the foregoing dithioacetal **49**, **49** was converted to the dimethyl acetal i by treatment with $Hg(ClO_4)_2$ in methanol–$CHCl_3$ and then was subjected to the reaction with benzyl bromide and KH. However, this sequence led to elimination instead of O-benzylation, thus generating the alkyne ii.



(36) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.
(37) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

Scheme XI[a]



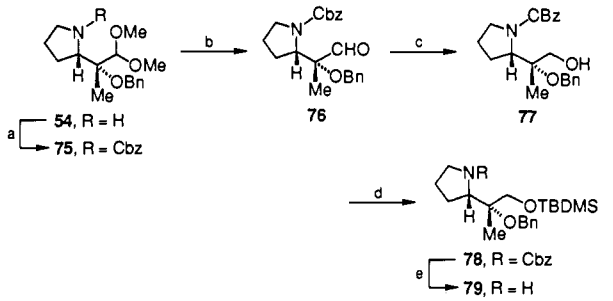
[a] (a) LDA, THF, −78 °C to 0 °C (83%); (b) $LiAlH_4$, THF, 0 °C (90%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (93%); (d) CBr_4 (2 equiv), PPh_3 (4 equiv), CH_2Cl_2, 0 °C (84%); (e) BuLi (2 equiv)/hexane, THF, $(HCHO)_n$, −78 °C to room temperature (92%); (f) Bu_3SnH (1.1 equiv), $PdCl_2(PPh_3)_2$ (2 mol %); (g) I_2, CH_2Cl_2, −78 °C to room temperature (98%); (h) CBr_4, PPh_3, CH_2Cl_2, 0 °C (98%).

regard, alkylation of the *N*-propionyl-(*S*)-oxazolidone **65**[38] with the allyl bromide **64** was conducted (LDA, THF, −78 °C) to provide **66** (83%) with virtually complete diastereoface selection. Reductive removal of the oxazolidinone auxiliary on **66** with $LiAlH_4$ afforded the alcohol **67** in 90% yield. After subjection of **67** to Swern oxidation, treatment of the resulting aldehyde **68** with CBr_4/PPh_3 furnished the dibromide **69** (78% overall yield from **67**), which was converted to the propargyl alcohol **70** (92% yield) by treatment with butyllithium (2 equiv) and paraformaldehyde. Stereospecific and highly regioselective syn hydrostannation of **70** was effected by applying palladium-catalyzed hydrostannation (1.1 equiv Bu_3SnH and 2 mol % $PdCl_2(PPh_3)_2$) under conditions similar to those described above. It furnished the (*E*)-2-(tributylstannyl)alkenyl alcohol **71** (93% yield) with none of the (*Z*)-isomer detectable, along with a minor amount of the 3-tributylstannyl regioisomer **72** (3.8%). Iododestannation was carried out by treatment of **71** with iodine to give exclusively the (*E*)-iodoalkene **73**, which was then transformed to the allyl bromide **74** in excellent overall yield (96% from **71**).

The preparation of the pyrrolidine segment **79** was attained from the foregoing pyrrolidine **54** in a straightforward manner, as outlined in Scheme XII. Compound **54** was successively converted to the alcohol **77** (77%) through N-protection by the Cbz group, acetal hydrolysis, and $NaBH_4$ reduction of the resulting aldehyde **76**. Silylation of **77** and hydrogenolytic removal of the Cbz group resulted in **79** (80% from **77**).

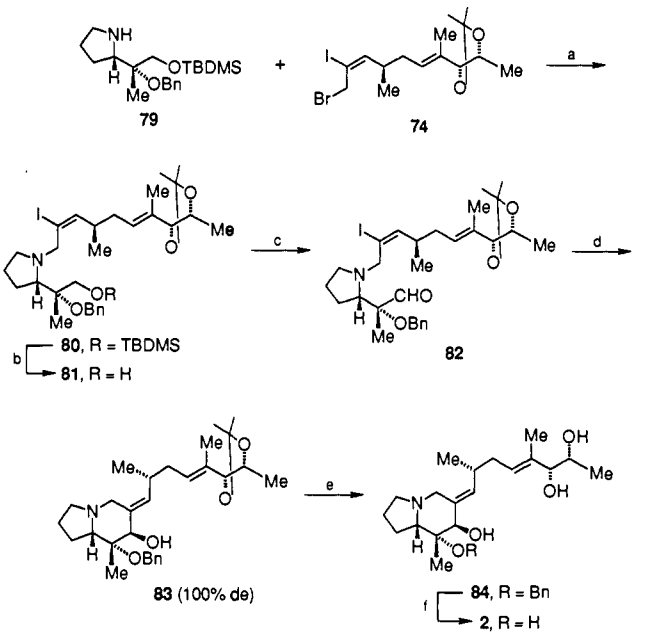
(38) Evans, D. A.; Bartroli, J.; Shih, T. L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Scheme XII[a]



[a] (a) CbzCl, Et_3N, CH_2Cl_2, 0 °C to room temperature (79%); (b) 3 N HCl/THF (99%); (c) $NaBH_4$, MeOH, room temperature (98%); (d) *t*-$BuMe_2SiCl$, imidazole, DMAP, CH_2Cl_2, room temperature (94%); (e) H_2, 10% Pd–C, MeOH (85%).

Scheme XIII[a]



[a] (a) *i*-Pr_2NEt, THF, room temperature (70%); (b) Bu_4NF, THF, room temperature (94%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (86%); (d) $CrCl_2$ (5 equiv), $NiCl_2$ (2.5 mol %), DMF, room temperature (79%); (e) 3 N HCl/THF, room temperature (91%); (f) Li, NH_3/THF, −78 °C (78%).

The final route that led to the successful preparation of (+)-allopumiliotoxin 339A (**2**) is summarized in Scheme XIII. Thus the segments **74** and **79** were coupled to provide **80** in 70% yield. Removal of the silyl protecting group followed by Swern oxidation gave the aldehyde **82** in 81% overall yield. On subsequent treatment with nickel(II)/chromium(II), intramolecular coupling of **82** proceeded smoothly to give exclusively **83** in 79% yield. The same stereochemical argument as described for **57** should hold for this process, thereby disposing the newly created hydroxy group anti to the preexisting benzyloxy group. Sequential removal of the isopropylidene protecting group under the acidic conditions and the benzyl group by treatment with Li/NH_3 provided (+)-allopumiliotoxin 339A (**2**) in 71% overall yield. Synthetic **2** had $[\alpha]^{28}_D$ +38.8° (*c* 0.5, MeOH) [lit.[2b] $[\alpha]^{25}_D$ +29.4° (*c* 1.0, MeOH)], and $[\alpha]^{28}_D$ +72.4° (*c* 0.66, $CHCl_3$) [lit.[4] $[\alpha]^{23}_D$ +68.2° (*c* 0.5, $CHCl_3$)] and exhibited spectral data (^1H and ^{13}C NMR) identical with those reported[2b] for the natural product.

In conclusion, we have established a highly stereocontrolled methodology for the enantioselective syntheses of allopumiliotoxin alkaloids 267A and 339A based on intramolecular nickel(II)/chromium(II)-mediated ring closure. The success of this methodology rests on the extremely high regio- and stereoselectivities observed through the overall sequences and are in particular

exhibited in a series of critical steps involving syn hydrostannation to the propargyl alcohols, construction of the exocyclic (*E*)-alkenyl moiety, and introduction of the trans diaxial diol into the indolizidine nucleus.

Experimental Section

General Procedures. All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Optical rotations were recorded on a JEOL DIP-4 instrument. IR spectra were taken with use of a Perkin-Elmer FTIR spectrometer. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were taken with use of a Varian Gemini-300, a Bruker AM-400, or an AM-500 spectrometer. Residual chloroform (7.26 ppm) was used as the internal reference for ^{1}H NMR spectra measured in $CDCl_3$. ^{13}C chemical shifts were reported on the δ scale relative to $CDCl_3$ as an internal reference (77.1 ppm). Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer at 70 eV. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC plates, and Merck silica gel 60 (230–400 mesh) was used for column chromatography.

1,1-Dibromo-3-methyl-1-butene (10). To a cooled (0 °C), stirred solution of isobutyraldehyde (3.17 g, 44.0 mmol) and triphenylphosphine (46.2 g, 176 mmol) in CH_2Cl_2 (150 mL) was added CBr_4 (29.2 g, 88.0 mmol) in small portions. After being stirred at the same temperature for 10 min, the mixture was washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL) and then dried ($MgSO_4$) and concentrated. To the residue was added Et_2O–hexane (1:1, 200 mL), and the solid was removed by filtration. The filtrate was concentrated, and the residual oil was purified by distillation under reduced pressure to give **10** (8.22 g, 82%) as a colorless oil: bp 65–66 °C (32 mmHg); IR (neat) 1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (6 H, d, J = 6.7 Hz, CH*Me*$_2$), 2.58 (1 H, m, C*H*Me$_2$), 6.21 (1 H, d, J = 9.1 Hz, CH=CBr_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (2 carbons), 33.2, 86.9, 145.1; EIMS m/z (relative intensity) 230 (M^+ + 4, 20), 228 (M^+ + 2, 42), 226 (M^+, 22), 215 (31), 213 (60), 211 (31), 199 (5), 185 (5), 165 (5), 149 (73), 147 (73), 133 (54), 131 (57), 119 (20), 107 (10), 93 (3), 83 (12), 67 (100); HRMS calcd for $C_5H_8{}^{79}Br_2$ (M^+) 225.8992, found 225.8999.

4-Methyl-2-pentyn-1-ol (11). To a solution of **10** (6.50 g, 28.5 mmol) in THF (60 mL) was added dropwise BuLi (36.6 mL of a 1.56 M solution in hexane, 57.1 mmol) at –78 °C under Ar. After the mixture was stirred at the same temperature for 1 h, a suspension of paraformaldehyde (1.71 g, 57.0 mmol) in THF (20 mL) was added to the above solution over 5 min, and the mixture was stirred at the same temperature for an additional 10 min. The mixture was allowed to warm to room temperature and stirred for 30 min, and then the reaction was quenched with brine (50 mL). The mixture was extracted with Et_2O (3 × 150 mL), and the extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by chromatography on silica gel with hexane–EtOAc (10:1) as eluent to give **11** (2.27 g, 81%) as a colorless oil: IR (neat) 3338, 2256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (6 H, d, J = 6.7 Hz, CH*Me*$_2$), 1.98 (1 H, br s, OH), 2.56 (1 H, m, C*H*Me$_2$), 4.22 (2 H, br d, J = 4.0 Hz, CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 22.9 (2 carbons), 51.2, 77.6, 91.9; EIMS m/z (relative intensity) 98 (M^+, 10), 97 916), 83 (90), 81 (10), 77 (12), 69 (52), 62 (10), 55 (99), 51 (37), 41 (100), 37 (5), 32 (36).

(*E*)-4-Methyl-2-(tributylstannyl)-2-penten-1-ol (12). To a stirred solution of **11** (1.88 g, 19.2 mmol) in THF (30 mL) was added $PdCl_2(PPh_3)_2$ (270 mg, 0.385 mmol) at room temperature. After the mixture was stirred for 5 min, Bu_3SnH (6.13 g, 21.1 mmol) was added dropwise to the mixture, and stirring was continued for 10 min. The mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (hexane–EtOH, 25:1). The first fraction afforded **12** (6.65 g, 89%) as a colorless oil: IR (neat) 3402, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.95 (21 H, m), 1.25–1.58 (12 H, m), 2.59 (1 H, m, C*H*Me$_2$), 4.37 (1 H, dd, J = 4.9, 1.8 Hz, J_{Sn-H} = 21 Hz, CH_2OH), 5.37 (1 H, dt, J = 9.0, 2.0 Hz, J_{Sn-H} = 34.9 Hz, CH=CSn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (3 carbons), 13.7 (3 carbons), 23.1, 27.1, 27.4 (3 carbons), 28.6, 29.2 (3 carbons), 63.5, 142.3, 148.2; EIMS m/z (relative intensity) 333 (M^+ – Bu, 21), 251 (100), 195 (10), 177 (24), 137 (56), 117 (20), 67 (4); HRMS calcd for $C_{14}H_{29}O^{120}Sn$ (M^+ – Bu) 333.1240, found 333.1258.

The second fraction afforded (*E*)-3-(tributylstannyl)-4-methyl-2-penten-1-ol (**13**) (284 mg, 3.8%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.97 (22 H, m), 1.27–1.53 (12 H, m), 2.93 (1 H, m, J_{Sn-H} = 42.9 Hz, C*H*Me$_2$), 4.26 (2 H, quint, J = 5.4 Hz, CH_2OH), 5.61 (1 H, td, J = 6.0, 1.0 Hz, J_{Sn-H} = 35.1 Hz, CH=CSn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (3 carbons), 13.7 (3 carbons), 23.8, 27.5 (3 carbons), 27.8, 29.1 (3 carbons), 31.9, 59.4, 137.1, 156.2.

(*E*)-2-Iodo-4-methyl-2-penten-1-ol (14). To a cold (–78 °C), stirred solution of **12** (5.46 g, 14.0 mmol) in CH_2Cl_2 (50 mL) was added a solution of I_2 (4.26 g, 16.8 mmol) in CH_2Cl_2 (20 mL) under Ar, and the resulting mixture was stirred at –78 °C for 15 min. After being warmed to room temperature, the mixture was stirred for an additional 15 min, washed with 10% $NaHSO_3$ followed by 10% KF, and dried ($MgSO_4$). Removal of the solvent in vacuo and purification by chromatography on silica gel (hexane–EtOAc, 10:1) gave **14** (3.00 g, 95%) as a colorless oil: IR (neat) 3349, 1628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (6 H, d, J = 6.7 Hz, CH*Me*$_2$), 2.71 (1 H, m, C*H*Me$_2$), 4.22 (2 H, dd, J = 6.5, 0.8 Hz, CH_2OH), 6.17 (1 H, br d, J = 9.8, Hz, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (2 carbons), 31.0, 65.2, 101.1, 150.7; CIMS (isobutane) m/z 226 (M^+), 209 (M^+ – OH); EIMS m/z (relative intensity) 226 (M^+, 20), 168 (3), 127 (16), 97 (4), 83 9100), 65 (12); HRMS calcd for $C_6H_{11}OI$ (M^+) 225.9855, found 225.9855.

(*E*)-1-Bromo-2-iodo-4-methyl-2-pentene (15). To an ice-cooled, stirred solution of **14** (800 mg, 3.54 mmol) and triphenylphosphine (1.86 g, 7.09 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (1.18 g, 8.56 mmol) under Ar, and the resulting mixture was stirred at 0 °C for 10 min. After evaporation of the solvent, Et_2O–hexane (1:1, 100 mL) was added to the residue, and the solid that separated was removed by filtration. The filtrate was condensed, and the residue was purified by chromatography on silica gel (hexane–EtOAc, 100:1) to give **15** (978 mg, 96%) as a colorless oil: IR (neat) 1619 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (6 H, d, J = 6.6 Hz, CH*Me*$_2$), 2.65 (1 H, m, C*H*Me), 4.30 (2 H, s, CH_2Br), 6.16 (1 H, d, J = 10.0 Hz, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (2 carbons), 31.1, 37.3, 92.7, 153.7; EIMS m/z (relative intensity) 290 (M^+ + 2, 10), 288 (M^+, 10), 250 (98), 209 936), 171 (24), 127 (10), 81 (38), 67 (16); HRMS calcd for $C_6H_{10}{}^{79}BrI$ (M^+) 287.9011, found 287.9019.

2-[2-(*tert*-Butyldimethylsiloxy)ethyl]piperidine (17). To an ice-cooled, vigorously stirred mixture of 2-piperidineethanol (**16**) (3.00 g, 23.2 mmol), CH_2Cl_2 (40 mL), and 20% aqueous Na_2CO_3 (25 mL) was added dropwise a solution of benzyl chloroformate (4.36 g, 25.6 mmol) in CH_2Cl_2 (5 mL). After being stirred for 1 h at the same temperature, the mixture was extracted with CH_2Cl_2 (3 × 80 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography on silica gel (hexane–EtOAc, 5:1) afforded *N*-[(benzyloxy)carbonyl]-2-(hydroxyethyl)piperidine (5.32 g, 87%) as a colorless oil: IR (neat) 3445, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–2.03 (8 H, m), 2.76 (1 H, t, J = 13.4 Hz), 3.38 91 H, br s), 3.56 (1 H, br s), 4.05 (1 H, br d, J = 12.8 Hz), 4.48 (1 H, br s), 5.12 and 5.15 (2 H, AB q, J = 12.6 Hz), 7.26–7.39 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 25.1, 28.7, 32.0, 38.9, 46.8, 58.3, 66.8, 127.4 (2 carbons), 127.6, 128.1 (2 carbons), 136.3, 156.0.

To a stirred solution of the above alcohol (5.19 g, 19.7 mmol), imidazole (1.74 g, 25.6 mmol), and 4-(dimethylamino)pyridine (DMAP) (121 mg, 0.990 mmol) in DMF (50 mL) was added *tert*-butylchlorodimethylsilane (3.86 g, 25.6 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was diluted with Et_2O (100 mL), washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent and column chromatography on silica gel (hexane–EtOAc, 20:1) gave *N*-[(benzyloxy)carbonyl]-2-[2-(*tert*-butyldimethylsiloxy)ethyl]piperidine (7.37 g, 99%) as a colorless oil: IR (neat) 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (6 H, s), 0.87 (9 H, s), 1.48 (1 H, m), 1.60 (5 H, m), 1.70 (1 H, td, J = 13.8, 6.5 Hz), 1.94 (1 H, m), 2.87 (1 H, br t, J = 12.8 Hz), 3.60 (2 H, m), 4.06 (1 H, br d, J = 11.9 Hz), 4.41 (1 H, m), 5.12 (2 H, s), 7.29–7.36 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.35, –5.32, 18.3, 19.1, 25.7, 26.0 (3 carbons), 28.7, 33.2, 39.4, 48.6, 60.9, 66.9, 127.8 (2 carbons), 127.9, 128.5 (2 carbons), 137.2, 155.5; CIMS (isobutane) m/z 378 (MH^+), 320. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.54; H, 9.53; N, 3.70.

To a solution of the above carbamate (2.97 g, 7.87 mmol) in MeOH (50 mL) was added 10% Pd–C (1.00 g), and the resulting suspension was vigorously stirred under 1 atm of H_2 for 16 h. After removal of the catalyst by filtration, the filtrate was concentrated, and the residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) to give **17** (1.82 g, 95%) as a colorless oil: IR (neat) 3359 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.88 (9 H, s), 1.12 (1 H, m), 1.27–1.62 (6 H, m), 1.76 (2 H, m), 2.60 (2 H, m), 3.02 (1 H, m), 3.70 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.25, –5.30,

18.3, 25.0, 26.0 (3 carbons), 26.6, 33.3, 40.0, 47.2, 55.1, 61.1; CIMS (isobutane) m/z 244 (MH^+), 228, 186; EIMS m/z (relative intensity) 243 (M^+, 3), 228 (M^+ – Me, 5), 186 (34), 156 (5), 110 (8), 98 (3), 84 (100), 73 (16); HRMS calcd for $C_{12}H_{26}NOSi$ (M^+ – Me) 228.1784, found 228.1788.

2-[2-(*tert*-Butyldimethylsiloxy)ethyl]-*N*-[(*E*)-2-iodo-4-methyl-2-pentene-1-yl]piperidine (18). A solution of **17** (768 mg, 3.16 mmol), **15** (826 mg, 2.87 mmol), and *i*-Pr_2NEt (556 mg, 4.30 mmol) in THF (7 mL) was stirred under Ar at room temperature for 16 h. The resulting mixture was diluted with Et_2O (30 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 50:1) to give **18** (1.09 g, 84%) as a colorless oil: IR (neat) 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Si^{t}Bu), 0.96 (6 H, d, J = 6.6 Hz, CHMe_2), 1.30–1.72 (8 H, m), 1.75–1.84 (1 H, m), 2.06 (1 H, m, 6-H_{ax}), 2.51 (1 H, m, 2-H), 2.71–2.81 (2 H, m, CHMe$_2$, 6-H_{eq}), 2.86 (1 H, A part of ABX, J = 13.8, 0.6 Hz, part of NCH_2C=), 3.36 (1 H, B part of ABX, J = 13.8, 1.1 Hz, part of NCH_2C=), 3.65–3.77 (2 H, m, OCH_2), 6.18 (1 H, d, J = 9.9 Hz, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2, –5.1, 18.3, 22.5, 22.6, 23.0, 24.8, 26.1 (3 carbons), 29.9, 31.2, 34.1, 49.7, 57.6, 60.9, 102.5, 150.5; CIMS (isobutane) m/z 452 (MH^+), 436, 394; EIMS m/z (relative intensity) 451 (M^+, 0.5), 436 (M^+ – Me, 2), 394 (M^+ – ^{t}Bu, 2), 324 (5), 292 (100), 243 (10), 186 (5), 166 (3), 122 (4); HRMS calcd for $C_{18}H_{35}NOISi$ (M^+ – Me) 436.1533, found 436.1523. Anal. Calcd for $C_{19}H_{38}NOISi$: C, 50.54; H, 8.48; N, 3.10. Found: C, 50.56; H, 8.59; N, 3.11.

2-(Formylmethyl)-*N*-[(*E*)-2-iodo-4-methyl-2-pentene-1-yl]piperidine (8). A mixture of **18** (840 mg, 1.86 mmol) and tetrabutylammonium fluoride (1.9 mL of a 1.0 M solution in THF, 1.90 mmol) was stirred at room temperature for 16 h. The resulting mixture was diluted with Et_2O (20 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 10:1) to give 2-(2-hydroxyethyl)-*N*-[(*E*)-2-iodo-4-methyl-2-pentene-1-yl]piperidine (508 mg, 81%) as a colorless oil: IR (neat) 3364, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.977 (3 H, d, J = 6.6 Hz, isopropyl Me), 0.982 (3 H, d, J = 6.7 Hz, isopropyl Me), 1.35–1.75 (7 H, m), 2.05 (1 H, m, 6-H_{ax}), 2.23 (1 H, m), 2.67–2.69 (2 H, m, CHMe$_2$, 2-H), 3.04 (1 H, ddd, J = 13.4, 9.0, 3.2 Hz, 6-H_{eq}), 3.26 (1 H, A part of ABX, J = 13.7, 0.5 Hz, part of NCH_2C=), 3.51 (1 H, B part of ABX, J = 13.7, 1.3 Hz, part of NCH_2C=), 3.78–3.90 (2 H, m, CH_2O), 6.22 (1 H, d, J = 10.0 Hz, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.2, 22.6, 22.7, 27.1, 31.3, 32.3, 47.2, 57.6, 59.6, 62.1, 100.3, 151.5; CIMS (isobutane) m/z 338 (MH^+); EIMS m/z (relative intensity) 337 (M^+, 1.2), 292 (99), 210 (3), 151 (3), 129 (34), 100 (3), 84 (100), 66 (16). Anal. Calcd for $C_{13}H_{24}NOI$: C, 46.30; H, 7.17; N, 4.15. Found: C, 46.66; H, 7.28; N, 4.03.

To a cold (–78 °C), stirred solution of oxalyl chloride (119 mg, 0.938 mol) in CH_2Cl_2 (3 mL) was added using a syringe DMSO (147 mg, 1.88 mmol), and the resulting mixture was stirred at –78 °C for 1 h. To this mixture was added using a syringe a solution of the above alcohol (158 mg, 0.469 mmol) in CH_2Cl_2 (2 mL) over 5 min at –78 °C. The mixture was stirred at –78 °C for 2 h. Triethylamine (285 mg, 2.82 mmol) was then added, and the mixture was warmed to room temperature. After addition of water (5 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ followed by brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 10:1) to give **8** (135 mg, 86%) as a colorless oil: IR (neat) 1722, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (6 H, d, J = 6.7 Hz, CHMe_2), 1.35–1.78 (6 H, m), 2.12 (1 H, m, 6-H_{ax}), 2.55 (1 H, A part of ABXX', J = 17.7, 6.6, 2.4 Hz, part of CH_2CHO), 2.62 (1 H, B part of ABXX', J = 17.7, 5.3, 2.4 Hz, part of CH_2CHO), 2.67–2.81 (2 H, m, CHMe$_2$, 2-H), 2.96 (1 H, A part of ABX, J = 13.7, 0.8 Hz, part of NCH_2C=), 3.03 (1 H, m, 6-H_{eq}), 3.27 (1 H, B part of ABX, J = 13.7, 1.3 Hz, part of NCH_2C=), 6.20 (1 H, br d, J = 10.0 Hz, C=CH), 9.88 (1 H, t, J = 2.4, Hz, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.49, 22.58, 22.60, 24.7, 30.8, 31.2, 45.4, 49.4, 55.3, 58.3, 100.8, 151.1, 202.5; CIMS (isobutane) m/z 336 (MH^+); EIMS m/z (relative intensity) 335 (M^+, 2), 292 (100), 210 (4), 180 (14), 164 (4), 127 918), 100 (4), 84 (89), 67 (18); HRMS calcd for $C_{13}H_{22}NOI$ (M^+) 335.0746, found 335.0762.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(2-pyridylthio)carbonyl]piperidine (20). A mixture of *N*-Boc-L-pipecolinic acid (**19**) (9.07 g, 39.6 mmol), 2,2'-dipyridyl sulfide (13.1, g 59.5 mmol), and triphenylphosphine (15.6 g, 59.5 mmol) in MeCN (150 mL) was refluxed for 1 h. After being cooled to room temperature, the mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (hexane–EtOAc, 10:1) to give **20** (12.0 g, 94%) as a pale yellow oil: $[\alpha]^{26}_D$ –50.9° (*c* 2.37, $CHCl_3$); IR (neat) 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35–1.85 (5 H, m), 1.51 (9 H, s, ^{t}Bu), 2.33 (1 H, br s), 3.05 (1 H, m, 6-H_{ax}), 4.11 (1 H, m, 6-H_{eq}), 4.93 and 5.14 (total 1 H, each br s, in 1:1 ratio, probably according to the rotamers, 2-H), 7.28 (1 H, br d, J = 5.7 Hz, 3-H in pyridine ring), 7.56–7.73 (2 H, m, 4-H and 5-H in pyridine ring), 8.63 (1 H, br s, 6-H in pyridine ring); FABMS m/z 323 (MH^+).

(2*S*)-2-Acetyl-*N*-(*tert*-butoxycarbonyl)piperidine (21). To an ice-cold, stirred solution of **20** (9.63 g, 29.9 mmol) in THF (90 mL) was added dropwise MeMgBr (34.3 mL of a 0.96 M solution in THF, 32.9 mmol) under Ar. After the mixture was stirred in an ice bath for 1.5 h, water (30 mL) was added to the mixture, and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **21** (6.12 g, 87%) as a colorless oil: $[\alpha]^{27}_D$ –43.4° (*c* 0.54, $CHCl_3$); IR (neat) 1723, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18–1.68 (5 H, m), 1.45 (9 H, br s, ^{t}Bu), 2.13 (3 H, s, MeCO), 2.17 (1 H, m), 2.84 (1 H, br s, 6-H_{ax}), 3.98 (1 H, m, 6-H_{eq}), 4.66 (1 H, m, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 25.0, 25.1, 26.7, 28.4, 42.7, 80.1, 155.6, 208.0; CIMS (isobutane) m/z 228 (MH^+), 212, 184; EIMS m/z (relative intensity) 184 (M^+ – COMe, 13), 155 (7), 128 (82), 110 (5), 84 (100). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31, N, 6.16. Found: C, 63.05; H, 9.47; N, 6.11.

(2*S*)-2-[(*R*)-1-(1,3-Dithian-2-yl)-1-hydroxyethyl]piperidine (22a) and (2*S*)-2-[(*S*)-1-(1,3-Dithian-2-yl)-1-hydroxyethyl]piperidine (22b). To a stirred solution of **21** (3.50 g, 12.6 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (4.32 g, 37.9 mmol). After being stirred at room temperature for 1 h, the solution was concentrated in vacuo to dryness, giving (2*S*)-acetylpiperidine trifluoroacetate. On the other hand, a solution of BuLi (48.1 mL of a 1.60 M solution in hexane, 77.0 mmol) was added dropwise to a cooled (–30 °C), stirred solution of 1,3-dithiane (9.25 g, 76.9 mmol) in THF (150 mL) under Ar over a period of 30 min. After being stirred at –30 °C to –20 °C for 1.5 h, the mixture was cooled to –78 °C. To this mixture was added dropwise a solution of the above trifluoroacetate salt in THF (30 mL), and the mixture was stirred at –78 °C for 1 h. After addition of water (50 mL), the mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel ($CHCl_3$–concentrated NH_4OH–MeOH, 350:9:1) gave a diastereomeric mixture of **22a** and **22b** (total 2.72 g, 72%) in a ratio of 6.2:1 (by ^1H NMR), which was recrystallized from Et_2O to afforded pure **22a** as colorless fine needles: mp 82–83 °C; $[\alpha]^{25}_D$ +0.30° (*c* 1.66, $CHCl_3$); IR (neat) 3422–3200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (3 H, s, CMe), 1.16–1.89 (7 H, m), 2.06 (1 H, m), 2.60 91 H, dt, J = 12.1, 2.9 Hz, 6-H_{ax}), 2.82–2.96 (5 H, m, 2 × SCH_2, 2-H), 3.12 (1 H, m, 6-H_{eq}), 4.34 (1 H, s, CHS_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.7, 26.1, 26.5, 26.6, 30.7, 31.0, 47.0, 57.7, 60.8, 75.9; CIMS (isobutane) m/z 248 (MH^+); EIMS m/z (relative intensity) 247 (M^+, 0.8), 229 (M^+ – H_2O, 3), 214 (1.4), 182 (1), 155 (2.4), 141 (4), 119 (18), 84 (100), 73 (3), 60 (6); HRMS calcd for $C_{11}H_{21}NOS_2$ (M^+) 247.1064, found 247.1049. Anal. Calcd for $C_{11}H_{21}NOS_2$: C, 53.40; H, 8.56; N, 5.66. Found: C, 53.19; H, 8.61; N, 5.86.

The mother liquid obtained in the above recrystallization was concentrated to give a solid, which was recrystallized from Et_2O to afford **22b** as colorless fine needles: mp 176–177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3 H, s, CMe), 1.28–1.98 (6 H, m), 2.05–2.15 (2 H, m), 2.66 (2 H, m), 2.85–2.95 (5 H, m, 2 × SCH_2, 2-H), 3.13 (1 H, m, 6-H_{eq}), 4.26 (1 H, s, CHS_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 24.7, 25.7, 26.1, 26.5, 30.8 (2 carbons), 47.3, 57.4, 62.9, 75.4; CIMS (isobutane) m/z 248 (MH^+); EIMS m/z (relative intensity) 247 (M^+, 2), 229 (M^+ – H_2O, 3), 214 (2.5), 182 (1.3), 164 (5), 119 (48), 106 (10), 84 (100), 73 (14), 60 (12).

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-[(*R*)-1-(1,3-dithian-2-yl)-1-hydroxyethyl]piperidine (23). To an ice-cold solution of **22a** (155 mg, 0.626 mmol) in CH_2Cl_2 (10 mL) was added 5% aqueous K_2CO_3 (10 mL), and the mixture was vigorously stirred. To this mixture was added benzyl chloroformate (160 mg, 0.938 mmol), and stirring was continued at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL), and the layers were separated. The organic layer was washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. The residual oil was subjected to column chromatography on silica gel (hexane–EtOAc, 10:1) to give **23** (210 mg, 88%) as a colorless oil: IR (neat) 3420, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (3 H, s, CMe), 1.20–2.10 (8 H, m), 2.77 (1 H, m, 6-H_{ax}), 2.65–3.04 (4 H, m), 3.44 (1 H, br s), 3.67 (1 H, br s), 4.12 (1 H, s, CHS_2), 5.16 (2 H, br s, CH_2Ph), 7.26–7.37 (5 H, m,

Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.9, 22.0, 23.6, 25.9, 30.4, 30.5, 43.6, 57.1, 61.4, 67.6, 78.5, 127.9, 128.0, 128.5, 136.6, 180.2; CIMS (isobutane) m/z 382 (MH^+), 362.

(2*S*)-2-[(*R*)1-(Dimethoxymethyl)-1-hydroxyethyl]piperidine (25). A solution of $Hg(ClO_4)_2 \cdot 3H_2O$ (10.2 g, 22.5 mmol) in MeOH (18 mL) was added dropwise to a stirred solution of **22a** (2.52 g, 10.2 mmol) in $CHCl_3$ (30 mL), and the mixture was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was basified with 10% aqueous K_2CO_3. After the organic solvent of the mixture was evaporated, the residue was extracted with $CHCl_3$ (3 × 30 mL), and the extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) gave **25** (1.57 g, 76%) as a colorless oil: $[\alpha]^{25}_D$ –0.99° (*c* 2.11, $CHCl_3$); IR (neat) 3446, 3339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3 H, s, CMe), 1.19–1.41 (3 H, m), 1.50–1.90 (H, m), 1.77–1.86 (1 H, m), 2.64 (1 H, dt, J = 11.9, 2.8 Hz, 6-H_{ax}), 2.70 (1 H, dd, J = 10.9, 2.6 Hz, 2-H), 3.05 (1 H, m, 6-H_{eq}), 3.50 (3 H, s, OMe), 3.55 (3 H, s, OMe), 4.16 (1 H, s, C*H*(OMe)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 24.5, 25.9, 26.1, 46.6, 57.9, 59.1, 59.3, 74.7, 111.6; CIMS (isobutane) m/z 204 (MH^+), 172.

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-[(*R*)-1-(dimethoxymethyl)-1-hydroxyethyl]piperidine (26). To an ice-cold solution of **25** (78.7 mg, 0.387 mmol) in CH_2Cl_2 (5 mL) was added 5% aqueous K_2CO_3 (4 mL), and the mixture was vigorously stirred. To this mixture was added benzyl chloroformate (85.9 mg, 0.503 mmol), and stirring was continued at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 (5 mL), and the organic layer that separated was washed with water (2 × 4 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 10:1) afforded **26** (120 mg, 92%) as a colorless oil: IR (neat) 3445, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3 H, s, CMe), 1.30–1.90 (6 H, m), 2.98–3.22 (1 H, m, 6-H_{ax}), 3.34 (3 H, br s, OMe), 3.45 (3 H, s, OMe), 3.81 (1 H, m, 2-H), 3.99 (1 H, s, C*H*(OMe)$_2$), 4.08 (1 H, br s, 6-H_{eq}), 5.01 and 5.08 (2 H, AB q, J = 13.7 Hz, CO_2CH_2Ph), 7.15–7.31 (5 H, m, Ph); EIMS m/z (relative intensity) 306 (M^+ – OMe, 1), 262 (22), 218 (16), 174 (30), 128 (3), 108 (4), 91 (100), 75 (71).

(1*R*,8a*R*)-1-(Dimethoxymethyl)-1-methyl-1,5,6,7,8,8a-hexahydrooxazolo[3,4-*a*]pyridin-3-one (27). To an ice-cold, stirred suspension of KH (30% in mineral oil, 43.5 mg, 0.380 mmol) in THF (2 mL) were added dropwise first a solution of **26** (98.6 mg, 0.292 mmol) in THF (5 mL) and then benzyl bromide (65.0 mg, 0.380 mmol). After being stirred at room temperature for 30 min, the mixture was diluted with Et_2O (40 mL). The Et_2O solution was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexane–EtOAc, 5:1) on silica gel to afford **27** (63.6 mg, 95%) as a colorless oil: IR (neat) 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3 H, s, CMe), 1.27–1.43 (3 H, m), 1.61–1.66 (2 H, m), 1.91 (1 H, m), 2.81 (1 H, m, 6-H_{ax}), 3.49 and 3.52 (each 3 H, s, OMe, attending 1 H due to 2-H (δ 3.47–3.54) at the base of these peaks), 3.83 (1 H, m, 6-H_{eq}), 4.12 (1 H, s, C*H*(OMe)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 23.2, 24.2, 26.5, 41.6, 57.58, 57.62, 58.3, 83.0, 108.8, 155.8; EIMS m/z (relative intensity) 229 (M^+, 2), 198 (M^+ – OMe, 1.3), 169 (5), 155 (3), 138 (18), 110 (7), 75 (100); HRMS calcd for $C_{11}H_{19}NO_4$ (M^+) 229.1314, found 229.1337.

(2*S*)-*N*-(Cyanomethyl)-2-[(*R*)-1-(dimethoxymethyl)-1-hydroxyethyl]-piperidine (28). To an ice-cold, stirred solution of **25** (941 mg, 4.63 mmol) in THF (5 mL) were added successively *i*-Pr_2NEt (778 mg, 6.02 mmol) and iodoacetonitrile (1.01 g, 6.05 mmol). The mixture was stirred at room temperature for 2.5 h and diluted with Et_2O (50 mL). The Et_2O solution was washed with water (10 mL) and brine (10 mL) and then dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 5:1) gave **28** (931 mg, 83%) as a pale yellow oil: $[\alpha]^{24}_D$ –13.1° (*c* 1.5, $CHCl_3$); IR (neat) 3495, 2235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3 H, s, CMe), 1.20–1.40 (2 H, m), 1.48–1.72 (4 H, m), 2.52 (1 H, s, OH), 2.58 (1 H, dd, J = 10.7, 2.8 Hz, 2-H), 2.64 (1 H, m, 6-H_{ax}), 2.86 (1 H, m, 6-H_{eq}), 3.42 (1 H, $^1/_2$ AB q, J = 17.0 Hz, part of CH_2CN), 3.50 (3 H, s, OMe), 3.56 (3 H, s, OMe), 4.19 (1 H, s, C*H*(OMe)$_2$), 4.39 (1 H, $^1/_2$ AB q, J = 17.0 Hz, part of CH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 23.6, 23.9, 24.9, 43.9, 54.7, 56.5, 58.5, 64.0, 77.9, 108.0, 117.2; CIMS (isobutane) m/z 243 (MH^+). Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.34; H, 9.20; N, 11.45.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]-*N*-(cyanomethyl)piperidine (29). To an ice-cold, stirred suspension of KH (30% in mineral oil, 371 mg, 2.77 mmol) in THF (3 mL) were added dropwise first a solution of **28** (517 mg, 2.13 mmol) in THF (5 mL) and then benzyl bromide (474 mg, 2.77 mmol). After being stirred at room temperature for 1 h, the mixture was diluted with Et_2O (50 mL). The Et_2O solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexane–EtOAc, 30:1) on silica gel to afford **29** (653 mg, 92%) as a colorless oil: $[\alpha]^{26}_D$ –12.0° (*c* 1.6, $CHCl_3$); IR (neat) 2240 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.26 (3 H, s, CMe), 1.40–1.43 (5 H, m), 1.85 (1 H, m), 2.73–2.82 (2 H, m, 2-H, 6-H_{ax}), 3.05 (1 H, m, 6-H_{eq}), 3.49 (1 H, $^1/_2$ AB q, J = 17.2 Hz, part of CH_2CN), 3.57 (3 H, s, OMe), 3.58 (3 H, s, OMe), 4.29 (1 H, $^1/_2$ AB q, J = 17.2 Hz, part of CH_2CN), 4.48 (1 H, s, C*H*(OMe)$_2$), 4.56 and 4.76 (2 H, AB q, J = 11.6 Hz, C*H*$_2$Ph), 7.22–7.38 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.3, 21.3, 24.6, 39.7, 53.3, 57.7, 58.8, 65.3, 66.3, 82.5, 109.9, 118.6, 127.2, 127.3 (2 carbons), 128.2 (2 carbons), 139.7; CIMS (isobutane) m/z 333 (MH^+), 306; EIMS m/z (relative intensity) 333 (MH^+, 0.3), 306 (M^+ – CN, 1), 241 (0.4), 226 (0.3), 194 (1), 163 (2), 140 (0.5), 123 (100), 91 (50), 75 (44); HRMS calcd for $C_{18}H_{28}NO_3$ (M^+ – CN) 306.2069, found 306.2068. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.27; H, 8.66; N, 8.36.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]piperidine (30). To a stirred solution of **29** (735 mg, 2.28 mmol) in EtOH (10 mL) was added $AgNO_3$ (774 mg, 4.56 mmol), and the mixture was stirred at room temperature for 1 h. The resulting suspension was filtered, and the filtrate was concentrated. Saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) to give **30** (603 mg, 93%) as a colorless oil: $[\alpha]^{27}_D$ +4.56° (*c* 1.6, $CHCl_3$); IR (neat) 3316 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3 H, s, CMe), 1.27–1.90 (6 H, m), 2.58 (1 H, dt, J = 12.5, 2.9 Hz, 6-H_{ax}), 2.74 (1 H, dd, J = 11.0, 2.3 Hz, 2-H), 3.12 (1 H, m, 6-H_{eq}), 3.53 (3 H, s, OMe), 3.54 (3 H, s, OMe), 4.49 (1 H, s, C*H*(OMe)$_2$), 4.59 and 4.69 (2 H, AB q, J = 11.6 Hz, C*H*$_2$Ph), 7.22–7.34 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 25.0, 26.8, 26.9, 47.1, 57.9, 58.0, 61.2, 65.8, 80.8, 109.5, 127.1, 127.3 (2 carbons), 128.3 (2 carbons), 140.1; CIMS (isobutane) m/z 294 (MH^+), 262; EIMS m/z (relative intensity) 294 (MH^+, 3), 218 (6), 178 (33), 135 (27), 84 (100), 64 (5); HRMS calcd for $C_{17}H_{28}NO_3$ (MH^+) 294.2069, found 294.2077.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]-*N*-[(*E*)-2-iodo-4-methyl-2-penten-1-yl]piperidine (31). A solution of **30** (502 mg, 1.71 mmol), **15** (640 mg, 2.22 mmol), and *i*-Pr_2NEt (332 mg, 2.57 mmol) in DMF (10 mL) was stirred under Ar at room temperature for 2 days. The resulting mixture was diluted with Et_2O (50 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 50:1) to give **31** (618 mg, 72%) as colorless crystals, a part of which was recrystallized from EtOAc to give colorless needles: mp 119–121 °C; $[\alpha]^{27}_D$ +9.90° (*c* 1.03, $CHCl_3$); IR (neat) 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (6 H, d, J = 6.6 Hz, CH*Me*$_2$), 1.25 (3 H, s, CMe), 1.22–1.30 (1 H, m), 1.40–1.60 (3 H, m), 1.72–1.93 (2 H, m), 2.55 (1 H, m, 6-H_{ax}), 2.71–2.84 (2 H, m, C*H*Me$_2$, 2-H), 3.02 (1 H, m, 6-H_{eq}), 3.53 (1 H, $^1/_2$ AB q, J = 14.5, 2.0 Hz, part of $NCH_2C{=}$), 3.61 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.79 (1 H, $^1/_2$ AB q, J = 14.5 Hz, part of $NHC_2C{=}$), 4.59 and 4.78 (2 H, AB q, J = 12.0 Hz, C*H*$_2$Ph), 5.13 (1 H, s, C*H*(OMe)$_2$), 6.17 (1 H, d, J = 9.9 Hz, C=CH), 7.20–7.33 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.4, 20.0, 22.7, 22.7, 24.9, 31.5, 48.6, 52.2, 58.0, 58.5, 66.2 (2 carbons), 82.6, 104.0, 108.9, 126.7, 126.8 (2 carbons), 128.1 (2 carbons), 140.8, 150.4; CIMS (isobutane) m/z 502 (MH^+), 470; EIMS m/z (relative intensity) 502 (M^+ + 1, 1), 470 (1.6), 425 (4), 373 (0.6), 334 (1), 292 (100), 210 (7), 164 (21), 122 (34); HRMS calcd for $C_{23}H_{36}NO_3I$ (M^+) 501.1740, found 501.1712. Anal. Calcd for $C_{23}H_{36}NO_3I$: C, 55.09; H, 7.24; N, 2.79. Found: C, 55.06; H, 7.31; N, 2.90.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-formylethyl]-*N*-[(*E*)-2-iodo-4-methyl-2-penten-1-yl]piperidine (9). To a cold (–78 °C), stirred solution of **31** (205 mg, 0.387 mmol) in CH_2Cl_2 (8 mL) was added dropwise BCl_3 (5.0 mL of a 1.0 M solution in CH_2Cl_2, 5.0 mmol), and the mixture was stirred at –78 °C. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), and CH_2Cl_2 (20 mL) was added to the mixture. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Purification by passing the residue through a short column of silica gel (hexane–EtOAc, 4:1) gave **9** (141 mg, 62%) as a pale yellow oil: IR (neat) 1733, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3 H, s, isopropyl Me), 0.96 (3 H, s, isopropyl Me), 1.42 (3 H, s, *Me*CCHO), 1.20–1.69 (5 H, m), 1.93 (1

H, m), 2.26 (1 H, m, 6-H_{ax}), 2.69 (1 H, m, C*H*Me_2), 2.82 (1 H, dd, J = 7.7, 4.4 Hz, 2-H), 3.09 (1 H, m, 6-H_{eq}), 3.31 (1 H, dd, J = 14.1, 0.8 Hz, part of NCH_2C=), 3.52 (1 H, dd, J = 14.1, 1.2 Hz, part of NCH_2C=), 4.44 and 4.51 (2 H, AB q, J = 11.5 Hz, CH_2Ph), 6.15 (1 H, d, J = 10.0 Hz, C=CH), 7.26–7.37 (5 H, m, Ph), 9.78 (1 H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 21.1, 22.5, 22.6, 22.7, 23.4, 31.3, 48.8, 56.9, 66.1, 66.5, 86.5, 101.7, 127.2 (2 carbons), 127.5, 128.4 (2 carbons), 138.6, 150.8, 204.1; CIMS (isobutane) m/z 456 (MH^+).

(2*S,9a*S**)- and (2*R**,9a*S**)-2-Hydroxy-3(*E*)-isobutylideneoctahydroquinolizine (33a and 33b).** To a stirred mixture of of $CrCl_2$ (244 mg, 1.99 mmol), $NiCl_2$ (1.3 mg, 0.010 mmol), and DMF (3 mL) under Ar was added a solution of **8** (133 mg, 0.397 mmol) in DMF (2 mL), and the mixture was stirred at room temperature for 3 h. After addition of saturated aqueous $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (3 × 20 mL), and the extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) afforded 67 mg (81%) of a diastereomeric mixture of **33a** and **33b** (1.3:1) as a colorless oil. The ratio of diastereomers was determined by ^{1}H NMR by comparing the intensities of C-2 protons: IR (neat) 3359, 2865, 2800–2700, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 6.7 Hz, isopropyl Me), 0.98 and 1.01 (total 3 H, 1.3:1 ratio, d, J = 6.6 Hz, isopropyl Me each), 1.15–2.33 (10 H, m), 2.38 and 2.80 (total 1 H, 1:1.3 ratio, $^1/_2$ AB q, J = 12.8 Hz, 4-H_{ax} each), 2.59 (1 H, m, C*H*Me_2), 2.86 (1 H, m, 6-H_{eq}), 3.38 and 3.59 (total 1 H, 1.3:1 ratio, $^1/_2$ AB q, J = 12.8 Hz, 4-H_{eq} each), 4.00 and 4.16 (total 1 H, 1:1.3 ratio, br s and dd, J = 10.4, 3.7 Hz, 2-H each), 5.23 and 5.30 (total 1 H, 1.3:1 ratio, d, J = 9.1 Hz and dt, J = 9.2, 1.5 Hz, C=CH each); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.35, 23.40, 23.7, 24.0, 24.5, 25.6, 25.7, 26.2, 26.3, 32.9, 40.5, 43.4, 52.0, 55.5, 55.9, 56.2, 56.5, 60.8, 70.8, 72.3, 127.7, 134.4, 135.1, 135.5; CIMS (isobutane) m/z 210 (MH^+), 192; EIMS m/z (relative intensity) 209 (M^+, 33), 194 (19), 192 (18), 176 (12), 166 (52), 151 (10), 136 (6), 122 (37), 108 (6), 93 (9), 84 (100), 66 (11); HRMS calcd for $C_{13}H_{23}NO$ (M^+) 209.1780, found 209.1771.

(1*R*,2*R*,9a*S*)-1-(Benzyloxy)-2-hydroxy-3(*E*)-isobutylidene-1-methyloctahydroquinolizine (35a). To a stirred mixture of $CrCl_2$ (281 mg, 2.29 mmol), $NiCl_2$ (1.5 mg, 0.012 mmol), and DMF (3 mL) under Ar was added a solution of **9** (208 mg, 0.457 mmol) in DMF (2 mL), and the mixture was stirred at room temperature for 20 h. A workup similar to that described above afforded a residue, which was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) to give **35a** (80 mg, 53%) as a colorless oil: $[\alpha]^{28}_D$ +1.81° (*c* 0.61, $CHCl_3$); IR (neat) 3320, 2866, 2800–2700, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 6.7 Hz, isopropyl Me), 1.01 (3 H, d, J = 6.6 Hz, isopropyl Me), 1.28 (3 H, s, 1-Me), 1.24–1.91 (6 H, m), 2.18 (1 H, dt, J = 11.9, 2.6 Hz, 6-H_{ax}), 2.40 (1 H, br d, J = 10.2 Hz, 9a-H), 2.55–2.71 (2H, m, C*H*Me, OH), 2.90 (1 H, br d, J = 12.9 Hz, 6-H_{eq}), 2.98 (1 H, d, J = 10.6 Hz, 4-H_{ax}), 3.50 (1 H, d, J = 12.9 Hz, 4-H_{eq}), 4.06 (1 H, s, 2-H), 4.53 (2 H, s, CH_2Ph), 5.32 (1 H, d, J = 9.1 Hz, C=CH), 7.20–7.35 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 23.0, 23.4, 23.6, 24.6, 24.9, 26.4, 50.8, 57.1, 64.3, 65.0, 76.2, 77.7, 127.0, 127.2 (2 carbons), 128.1 (2 carbons), 136.4, 140.2; CIMS (isobutane) m/z 330 (MH^+), 312, 238; EIMS m/z (relative intensity) 291 (2), 260 91.3), 238 (M^+ – Bn, 84), 225 (5), 206 95), 190 (6), 166 (10), 140 (36), 122 (7), 106 (7), 91 (100), 65 (14); HRMS calcd for $C_{14}H_{24}NO_2$ (M^+ – Bn) 238.1807, found 238.1790.

(2*S*,3*S*)-1-Chloro-2,3-epoxyheptane (37). A solution of **36** (21.7 g, 0.167 mol) and triphenylphosphine (52.5 g, 0.200 mol) in CCl_4 (150 mL) was refluxed for 3.5 h. After the solution was cooled to room temperature, Et_2O (50 mL) was added to the mixture, and the solid that separated was removed by filtration. The filtrate was concentrated to give an oil, which was purified by distillation to afford **37** (22.8 g, 92%) as a colorless oil: bp 85–89 °C (25 mmHg); $[\alpha]^{28}_D$ –11.4° (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3 H, t, J = 7.2 Hz, 7-Me), 1.34–1.61 (6 H, m, -$(CH_2)_3$-), 2.86 (1 H, t, J = 5.6 Hz, 3-H), 2.98 (1 H, t, J = 5.6 Hz, 2-H), 3.49 (1 H, dd, J = 11.6, 5.6 Hz, CHCl), 3.58 (1 H, dd, J = 11.6, 5.6 Hz, CHCl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 28.0, 31.4, 44.8, 57.2, 59.1; EIMS m/z (relative intensity) 113 (M^+ – Cl, 34), 104 (5), 95 (6), 79 (7), 69 (100), 63 (3); HRMS calcd for $C_7H_{13}O$ (M^+ – Cl) 113.0966, found 113.0970.

(*S*)-1-Heptyn-3-ol (38). To a cold (–35 °C), stirred solution of **37** (13.6 g, 91.5 mmol) in THF (100 mL) was added dropwise BuLi (165 mL of a 1.66 M solution in hexane, 274 mmol) under Ar. The mixture was stirred at the same temperature for 1 h, quenched with water (100 mL), and extracted with Et_2O (3 × 200 mL). The extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by distillation to give **38** (9.34 g, 91%) (94% ee by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester) as a colorless oil: bp 73–78 °C (22 mmHg) (lit.[33] bp 76 °C (25 mmHg)); $[\alpha]^{28}_D$ –17.8° (*c* 1.8, dioxane) (lit.[33] $[\alpha]^{25}_D$ –18.8° (*c* 5.2, dioxane, >98% ee)); IR (neat) 3311, 2116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, t, J = 7.2 Hz, 7-Me), 1.31–1.49 (4 H, m, -$(CH_2)_2$-), 1.69 (2 H, m, -CH_2-), 1.81 (1 H, d, J = 5.2 Hz, OH), 2.46 (1 H, d, J = 2.1 Hz, 1-H), 4.37 (1 H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 27.2, 37.4, 62.4, 72.8, 85.1; EIMS m/z (relative intensity) 111 (M^+ – 1, 4), 97 (16), 91 (9), 83 (72), 77 (15), 70 (100), 65 (10), 60 (7); HRMS calcd for $C_7H_{11}O$ (M^+ – 1) 111.0810, found 111.0823.

(*R*)-3-Methyl-1-heptyne (40). A mixture of **39** (6.50 g, 35.6 mmol) and Bu_4NF (71.3 mL of a 1.0 M solution in THF, 71.3 mmol) was stirred at room temperature for 6 h. To this mixture was added 3 N HCl (50 mL), and the mixture was extracted with pentane (3 × 100 mL), washed successively with saturated aqueous $NaHCO_3$ and brine, and then dried ($MgSO_4$). The solvent was carefully removed by evaporation, and the residue was purified by distillation to give **40** (3.42 g, 87%) as a colorless oil: bp 92–97 °C; $[\alpha]^{26}_D$ –25.3° (*c* 1.7, $CHCl_3$); IR (neat) 2111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3 H, t, J = 7.2 Hz, 7-Me), 1.18 (3 H, d, J = 7.0 Hz, C_3-Me), 1.30–1.50 (6 H, m, -$(CH_2)_3$-), 2.02 (1 H, d, J = 2.4 Hz, 1-H), 2.42 (1 H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.0, 22.5, 25.7, 29.5, 36.5, 68.0, 89.4; EIMS m/z (relative intensity) 109 (M^+ – 1, 1), 95 (85), 81 (62), 68 (100); HRMS calcd for C_8H_{14} (M^+) 110.1096, found 110.1100.

(*R*)-4-Methyl-2-octyn-1-ol (41). To a cold (–78 °C), stirred solution of **40** (5.29 g, 48.0 mmol) in THF (50 mL) was added a solution of BuLi (30.2 mL of a 1.59 M solution in hexane, 48.0 mmol) under Ar, and the mixture was stirred for 30 min. After a suspension of paraformaldehyde (2.88 g, 95.9 mmol as HCHO) in THF (20 mL) was added, the mixture was allowed to warm to room temperature, and stirring was continued for 45 min. The mixture was filtered through a Celite pad, and brine (30 mL) was added to the filtrate. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by column chromatography on silica gel (hexane–EtOAc, 8:1) to give **41** (5.72 g, 85%) (88% ee by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester) as a colorless oil: $[\alpha]^{26}_D$ –32.9° (*c* 2.5, $CHCl_3$); IR (neat) 3328, 2233 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3 H, t, J = 7.2 Hz, 8-Me), 1.15 (3 H, d, J = 7.0 Hz, C_4-Me), 1.30–1.44 (6 H, m, -$(CH_2)_3$-), 1.49 (1 H, t, J = 6.0 Hz, OH), 2.40–2.49 (1 H, m, 4-H), 4.26 (2 H, dd, J = 6.0, 2.0 Hz, 1-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.0, 22.6, 25.9, 29.6, 36.6, 51.5, 78.4, 91.1; CIMS (isobutane) m/z 139 (MH^+), 123, 109; EIMS m/z (relative intensity) 125 (M^+ – Me, 3), 128 (5), 109 (M^+ – CH_2OH, 75), 97 (33), 91 (14), 83 (55), 77 (24), 66 (100); HRMS calcd for $C_8H_{13}O$ (M^+ – Me) 125.0966, found 125.0990.

(*E*)-(*R*)-4-Methyl-2-(tributylstannyl)-2-octen-1-ol (42). A mixture of **41** (3.05 g, 21.8 mmol), $PdCl_2(PPh_3)_2$ (306 mg, 0.436 mmol), and THF (30 mL) under Ar was stirred at room temperature for 5 min, and Bu_3SnH (6.96 g, 23.9 mmol) was added dropwise to the mixture of a period of 5 min. The resulting mixture was stirred at room temperature for 10 min and concentrated in vacuo to give an oily residue, which was subjected to column chromatography on silica gel (hexane–EtOAc, 20:1). The first fraction furnished **42** (8.73 g, 93%) as a pale yellow oil: $[\alpha]^{28}_D$ –19.3° (*c* 1.1, $CHCl_3$); IR (neat) 3442, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.94 (21 H, m), 1.14–1.60 (18 H, m), 2.37–2.48 (1 H, m, 4-H), 4.35 (2 H, m, 2-H_2), 5.30 (1 H, dt, J = 9.4, 1.9 Hz, J_{Sn-H} = 35.2 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (3 carbons), 11.8, 13.8 (3 carbons), 14.1, 21.3, 22.9, 27.4 (3 carbons), 29.2 (3 carbons), 29.9, 33.9, 37.2, 63.8, 143.0, 147.4; EIMS m/z (relative intensity) 375 (M^+ – Bu, 21), 353 (9), 251 (100), 177 (19), 141 (10), 137 (50), 117 (17), 95 (4), 67 (11); HRMS calcd for $C_{17}H_{35}O^{120}Sn$ (M^+ – Bu) 375.1710, found 375.1707.

The second fraction furnished (*E*)-(*R*)-4-methyl-3-(tributylstannyl)-2-octen-1-ol (**43**) (0.15 g, 1.6%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.95 (21 H, m), 1.14–1.60 (18 H, m), 2.65–2.78 (1 H, m, 4-H), 4.24 (2 H, m, 1-H_2), 5.67 (1 H, td, J = 7.0, 1.0 Hz, J_{Sn-H} = 35.4 Hz, 2-H).

(*E*)-(*R*)-2-Iodo-4-methyl-2-octen-1-ol (44). To an ice-cold, stirred solution of **42** (8.54 g, 19.8 mmol) in CH_2Cl_2 (85 mL) was added dropwise a solution of iodine (6.03 g, 23.8 mmol) in CH_2Cl_2 (180 mL) under Ar over a period of 30 min. The mixture was allowed to warm to room temperature, stirred for another 30 min, and washed with 10% aqueous $NaHSO_3$ and then with 10% aqueous KF. Drying ($MgSO_4$) and evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to furnish

44 (5.20 g, 98%) (84% ee by ^1H NMR analysis of the corresponding (*S*)-MTPA ester) as a colorless oil: $[\alpha]^{28}_D$ −36.1° (*c* 1.0, $CHCl_3$); IR (neat) 3349, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 7.3 Hz, 8-Me), 0.98 (3 H, d, *J* = 6.7 Hz, C_4-Me), 1.19–1.42 (6 H, m, $-(CH_2)_3-$), 1.76 (1 H, t, *J* = 6.6 Hz, OH), 2.50–2.55 (1 H, m, 4-H), 4.21 (2 H, d, *J* = 6.6 Hz, 1-H_2), 6.11 (1 H, d, *J* = 10.2 Hz, 3-H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 14.0, 20.8, 22.7, 29.6, 36.4, 36.7, 65.3, 101.5, 149.9; EIMS *m/z* (relative intensity) 268 (M^+, 4), 207 (1), 123 (15), 101 (100), 84 (60), 67 (21); HRMS calcd for $C_9H_{17}OI$ (M^+) 268.0324, found 268.0338.

(*E*)-(*R*)-1-Bromo-2-iodo-4-methyl-2-octene (45). To a stirred solution of **44** (1.26 g, 4.70 mmol) and triphenylphosphine (2.47 g, 9.42 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (3.12 g, 9.41 mmol) with ice-cooling. After the solution was stirred for 10 min and concentrated in vacuo, Et_2O–hexane (1:1, 100 mL) was added to the residue, and the resulting solid was filtered. The filtrate was condensed, and the residue was purified by chromatography on silica gel (hexane) to give **45** (1.54 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ −10.3° (*c* 1.2, $CHCl_3$); IR (neat) 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3 H, t, *J* = 6.9 Hz, 8-Me), 1.01 (3 H, d, *J* = 6.7 Hz, C_4-Me), 1.21–1.42 (6 H, m, $-(CH_2)_3-$), 2.42–2.53 (1 H, m, 4-H), 4.26 and 4.30 (2 H, AB q, *J* = 11.0 Hz, 1-H_2), 6.12 (1 H, d, *J* = 10.3 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.0, 22.7, 29.6, 36.3, 36.5, 37.5, 93.1, 153.1; EIMS *m/z* (rel intensity) 332 (M^+ + 2, 3), 330 (M^+, 3), 275 (3), 273 (3), 253 (63), 251 (64), 195 (3), 172 (9), 146 (11), 123 (100), 83 (12), 67 (68); HRMS calcd for $C_9H_{16}{}^{79}BrI$ (M^+) 329.9483, found 329.9494.

(2*S*)-2-[(*R*)-1-(1,3-Dithian-2-yl)-1-hydroxyethyl]pyrrolidine (48). According to the reported procedure,[3,4] **46** (4.32 g, 20.3 mmol) was deprotected by treatment with CF_3CO_2H (6.93 g, 60.8 mmol) in CH_2Cl_2 (30 mL) at room temperature to give the trifluoroacetate salt of **47**, which was subjected to further reaction as follows. A solution of BuLi (62.5 mL of a 1.62 M solution in hexane, 101 mmol) was added to a cooled (−30 °C), stirred solution of 1,3-dithiane (12.2 g, 101 mmol) in THF (150 mL) under Ar over a period of 30 min. After being stirred at −30 °C to −20 °C for 1.5 h, the mixture was cooled to −78 °C. To this mixture was added dropwise a solution of the above **47** trifluoroacetate (4.60 g, 20.2 mmol) in THF (30 mL), and the mixture was stirred at −78 °C for 30 min. After addition of water (50 mL), the mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) gave a colorless oil, which was solidified by triturating to provide **48** (2.55 g, 54%): mp 60–62 °C; $[\alpha]^{26}_D$ −33.3° (*c* 1.9, $CHCl_3$); IR (neat) 3322 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3 H, s, CMe), 1.58–1.90 (5H, m), 2.03–2.12 (1 H, m), 2.77–2.92 (7 H, m, $-SCH_2CH_2CH_2S-$, part of 5-H_2, NH, OH), 2.95–3.12 (1 H, m, part of 5-H_2), 3.49 (1 H, br t, *J* = 7.6 Hz, 2-H), 4.24 (1 H, s, CHS_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 26.2, 26.28, 26.34, 30.9, 31.3, 47.0, 59.9, 62.0, 74.2; EIMS *m/z* (relative intensity) 233 (M^+, 0.4), 215 ($M^+ - H_2O$, 0.4), 200 (0.4), 188 (2), 173 (1), 160 (0.5), 147 (0.4), 136 (1), 114 (4), 83 (24), 70 (100); HRMS calcd for $C_{10}H_{19}NOS_2$ (M^+) 233.0908, found 233.0929. Anal. Calcd for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00. Found: C, 51.44; H, 8.07; N, 6.10.

(2*S*)-2-[(*R*)-1-(1,3-Dithian-2-yl)-1-hydroxyethyl]-*N*-[(*E*)-(*R*)-2-iodo-4-methyl-2-octenyl]pyrrolidine (49). A solution of **48** (251 mg, 1.08 mmol), **45** (463 mg, 1.40 mmol), and *i*-Pr_2NEt (209 mg, 1.62 mmol) in THF (10 mL) was stirred under Ar at room temperature for 2 days. The mixture was diluted with Et_2O (100 mL), washed with brine, and dried ($MgSO_4$). The solvent was removed, and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to provide **49** (338 mg, 65%) as a pale yellow oil: $[\alpha]^{27}_D$ −52.6° (*c* 1.4, $CHCl_3$); IR (neat) 3500, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 6.8 Hz, 8′-Me), 0.97 (3 H, d, *J* = 6.6 Hz, $C_{4'}$-Me), 1.22 (3 H, s, *Me*COH), 1.15–1.35 (6 H, m, $(CH_2)_3CH_3$), 1.62–1.91 (5 H, m), 2.05–2.15 (1 H, m), 2.31–2.38 (1 H, m, part of 5-H_2), 2.50–2.60 (1 H, m, 4′-H), 2.79–3.06 (6 H, m, part of 5-H_2, $-SCH_2CH_2CH_2S-$, OH), 3.28 (1 H, br t, *J* = 6.9 Hz, 2-H), 3.35 (2 H, s, 1′-H_2), 4.78 (1 H, s, CHS_2), 6.09 (1 H, d, *J* = 10.2 Hz, 3′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.8, 20.5, 22.7, 25.1, 26.3, 27.9, 29.5, 30.8, 30.9, 36.6, 36.7, 54.0, 58.2, 61.5, 66.9, 76.9, 103.7, 149.3; CIMS (isobutane) *m/z* 484 (MH^+); EIMS *m/z* (relative intensity) 484 (M^+ + 1, 9), 320 (100), 119 (19). Anal. Calcd for $C_{19}H_{34}NOIS_2$: C, 47.21; H, 7.09; N, 2.90. Found: C, 47.38; H, 7.11; N, 3.13.

(2*S*)-2-[(*R*)-1-Hydroxy-1-formylethyl]-*N*-[(*E*)-(*R*)-2-iodo-4-methyl-2-octenyl]pyrrolidine (50). To a stirred solution of **49** (285 mg, 0.59 mmol) in THF (5 mL) was added dropwise a solution of $Hg(ClO_4)_2 \cdot 3H_2O$ (802 mg, 1.77 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was basified with 10% aqueous K_2CO_3 and concentrated in vacuo. The residue was extracted with Et_2O (3 × 50 mL), and the Et_2O solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel (hexane–EtOAc, 4:1) gave **50** (220 mg, 95%) as a colorless oil: IR (neat) 3424, 1729, 1634, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* = 7.0 Hz, 8′-Me), 0.95 (3 H, d, *J* = 6.6 Hz, $C_{4'}$-Me), 1.20 (3 H, s, *Me*COH), 1.10–1.37 (6 H, m, $(CH_2)_3Me$), 1.60–1.94 (4 H, m), 2.23–2.31 (1 H, m, part of 5-H_2), 2.54 (1 H, m, 4′-H), 2.96–3.45 (4 H, m, 2-H, 1′-H_2, part of 5-H_2), 6.04 (1 H, dd, *J* = 10.4, 0.9 Hz, 3′-H), 9.92 (1 H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.0, 20.5, 22.8, 24.3, 27.0, 29.6, 36.6, 36.7, 53.8, 59.8, 67.6, 79.1, 107.1, 149.4, 208.8; EIMS *m/z* (relative intensity) 394 (M^+ + 1, 2), 364 (M^+ − CHO, 29), 320 (100), 248 (3), 196 (5), 149 (10), 126 (16), 108 (10).

(2*S*)-2-[(*R*)-1-(Dimethoxymethyl)-1-hydroxyethyl]pyrrolidine (51). To a stirred solution of **48** (1.54 g, 6.60 mmol) in $CHCl_3$ (30 mL) was added dropwise a solution of $Hg(ClO_4)_2 \cdot 3H_2O$ (6.58 g, 14.5 mmol) in MeOH (18 mL), and the mixture was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was basified with 10% aqueous K_2CO_3 and concentrated in vacuo. The residue was extracted with $CHCl_3$ (100 mL), and the $CHCl_3$ solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) gave **51** (850 mg, 68%) as a colorless oil: $[\alpha]^{26}_D$ −24.6° (*c* 0.88, $CHCl_3$); IR (neat) 3349–3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (3 H, s, *Me*COH), 1.54–1.79 (4 H, m, 3-H_2, 4-H_2), 2.95–3.00 (2 H, m, 5-H_2), 3.25–3.30 (1 H, m, 2-H), 3.50 (3 H, s, OMe), 3.53 (3 H, s, OMe), 4.03 (1 H, s, C*H*$(OMe)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 24.5, 26.0, 46.2, 58.1, 58.6, 61.2, 73.2, 112.0; FABMS *m/z* 190 (MH^+).

(2*S*)-*N*-(Cyanomethyl)-2-[(*R*)-1-(dimethoxymethyl)-1-hydroxyethyl]-pyrrolidine (52). To an ice-cold, stirred solution of **51** (795 mg, 4.20 mmol) in THF (5 mL) was added successively Et_3N (552 mg, 5.46 mmol) and iodoacetonitrile (912 mg, 5.46 mmol). The mixture was stirred at room temperature for 2.5 h and diluted with Et_2O (50 mL). The Et_2O solution was washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 4:1) gave **52** (853 mg, 89%) as a pale yellow oil: $[\alpha]^{27}_D$ −50.2° (*c* 1.6, $CHCl_3$); IR (neat) 3501, 2232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3 H, s, *Me*$CCHO_2$), 1.68–1.92 (4 H, m, 3-H_2, 4-H_2), 2.61 (1 H, br s, OH), 2.70 (1 H, m, part of 5-H_2), 2.97–3.06 (2 H, m, 2-H, part of 5-H_2), 3.50 (3 H, s, OMe), 3.51 (3 H, s, OMe), 3.64 (1 H, $^1/_2$ AB q, *J* = 17.2 Hz, part of CH_2CN), 4.00 (1 H, s, C*H*$(OMe)_2$), 4.04 (1 H, $^1/_2$ AB q, *J* = 17.2 Hz, part of CH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 24.3, 27.7, 43.4, 54.8, 57.8, 57.9, 65.3, 76.6, 110.1, 117.1; EIMS *m/z* (relative intensity) 229 (M^+ + 1, 0.2), 228 (M^+, 0.1), 202 (M^+ − CN, 1), 181 (0.2), 170 (0.4), 153 (6), 126 (8), 109 (100), 75 (40); HRMS calcd for $C_{11}H_{20}N_2O_3$ (M^+) 228.1474, found 228.1480. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.56; H, 8.70; N, 12.09.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]-*N*-(cyanomethyl)pyrrolidine (53). To an ice-cold, stirred suspension of KH (35% in mineral oil, 509 mg, 4.44 mmol) in THF (10 mL) were added dropwise first a solution of **52** (782 mg, 3.43 mmol) in THF (5 mL) and then benzyl bromide (762 mg, 4.46 mmol). After being stirred at room temperature for 30 min, the mixture was refluxed for 2 h, cooled to room temperature, and diluted with Et_2O (100 mL). The Et_2O solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexane–EtOAc, 100:1) on silica gel to afford **53** (993 mg, 91%) as a pale yellow oil: $[\alpha]^{27}_D$ −33.1° (*c* 1.8, $CHCl_3$); IR (neat) 2229, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3 H, s, *Me*COBn), 1.75–1.98 (4 H, m, 3-H_2, 4-H_2), 2.65–2.73 (1 H, m, part of 5-H_2), 3.04–3.14 (2 H, m, 2-H, part of 5-H_2), 3.52 (3 H, s, OMe), 3.58 (3 H, s, OMe), 3.62 and 3.93 (2 H, AB q, *J* = 17.1 Hz, CH_2CN), 4.25 (1 H, s, C*H*$(OMe)_2$), 4.66 and 4.78 (2 H, AB q, *J* = 11.6 Hz, CH_2Ph), 7.23–7.40 (5 H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 24.2, 27.6, 43.9, 54.5, 57.1, 57.6, 65.8, 66.1, 82.9, 109.4, 117.1, 127.1, 127.2 (2 carbons), 128.2 (2 carbons), 139.5; EIMS *m/z* (relative intensity) 319 (M^+ + 1, 4), 292 (M^+ − CN, 13), 227 (M^+ − Bn, 6), 195 (3), 180 (17), 165 (5), 149 (14), 126 (6), 109 (100), 91 (42), 75 (34); HRMS calcd for $C_{18}H_{26}N_2O_3$ (M^+) 318.1944, found 318.1927. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.88; H, 8.16; N, 8.79.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]pyrrolidine (54). To a stirred solution of **53** (735 mg, 2.31 mmol) in EtOH (10 mL) was

added $AgNO_3$ (784 mg, 4.62 mmol), and the mixture was stirred at room temperature for 1 h. The resulting suspension was filtered, and the filtrate was concentrated. Saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) to give **54** (613 mg, 95%) as a pale yellow oil: $[\alpha]^{26}_D$ −19.9° (*c* 0.65, $CHCl_3$); IR (neat) 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (3 H, s, *Me*COBn), 1.70–1.90 (4 H, m, 3-H_2, 4-H_2), 3.01 (2 H, br t, *J* = 6.6 Hz, 5-H_2), 3.43–3.49 (1 H, m, 2-H), 3.58 (3 H, s, OMe), 3.59 (3 H, s, OMe), 4.49 (1 H, s, C*H*$(OMe)_2$), 4.62 and 4.73 (2 H, AB q, *J* = 11.4 Hz, C*H*$_2$Ph), 4.98 (1 H, br s, NH), 7.24–7.38 (5 H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 25.2, 26.3, 47.1, 58.1, 58.5, 64.1, 66.0, 78.7, 109.8, 127.1 (2 carbons), 127.3, 128.3 (2 carbons), 139.4; EIMS *m/z* (relative intensity) 280 (M^+ + 1, 0.8), 204 (M^+ − CH$(OMe)_2$, 3), 178 (21), 135 (27), 91 (49), 70 (100); HRMS calcd for $C_{16}H_{26}NO_3$ (M^+ + 1) 280.1913, found 280.1910.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(dimethoxymethyl)ethyl]-*N*-[(*E*)-(*R*)-2-iodo-4-methyl-2-octenyl]pyrrolidine (55). A solution of **45** (331 mg, 1.00 mmol), **54** (215 mg, 0.771 mmol), and *i*-Pr_2NEt (174 mg, 1.35 mmol) in THF (5 mL) under Ar was stirred at room temperature for 2 days. The mixture was diluted with Et_2O (50 mL), washed with brine, and dried ($MgSO_4$). The solvent was removed, and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to provide **55** (281 mg, 69%) as a pale yellow oil: $[\alpha]^{27}_D$ −61.9° (*c* 1.0, $CHCl_3$); IR (neat) 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 6.9 Hz, 8′-Me), 0.91 (3 H, d, *J* = 6.7 Hz, C$_{4'}$-Me), 1.15–1.35 (6 H, m, (C*H*$_2$)$_3$Me), 1.30 (3 H, s, *Me*COBn), 1.55–1.88 (4 H, m, 3-H_2, 4-H_2), 2.25 (1 H, dt, *J* = 10.1, 6.7 Hz, part of 5-H_2), 2.57 (1 H, m, 4′-H), 2.90–2.98 (2 H, m, 2-H, part of 5-H_2), 3.16 (1 H, d, *J* = 13.7 Hz, part of 1′-H_2), 3.43 (1 H, dd, *J* = 13.7, 1.7 Hz, part of 1′-H_2), 3.54 (3 H, s, OMe), 3.57 (3 H, s, OMe), 4.69 (1 H, s, C*H*$(OMe)_2$), 4.72 and 4.85 (2 H, AB q, *J* = 11.5 Hz, C*H*$_2$PH), 6.10 (1 H, br d, *J* = 9.4 Hz, 3′-H), 7.19–7.41 (5 H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.6, 20.8, 22.8, 24.1, 27.2, 29.7, 36.5, 36.9, 53.0, 56.9, 58.4, 60.6, 66.1, 68.6, 82.8, 104.2, 109.6, 126.8, 127.3 (2 carbons), 128.1 (2 carbons), 140.4, 148.9; EIMS *m/z* (relative intensity) 530 (M^+ + 1, 0.3), 529 (M^+, 0.1), 454 (M^+ − CH$(OMe)_2$, 1.4), 402 (0.3), 362 (0.9), 320 (100); HRMS calcd for $C_{25}H_{40}NO_3I$ (M^+) 529.2053, found 529.2016. Anal. Calcd for $C_{25}H_{40}NO_3I$: C, 56.71; H, 7.61; N, 2.65. Found: C, 56.54; H, 7.57; N, 2.62.

Further chromatographic separation with the same solvent system provided the more polar *N*-[(*E*)-(*S*)-2-iodo-4-methyl-2-octenyl] diastereomer (25 mg, 6%) as a pale yellow oil: $[\alpha]^{27}_D$ +43.5° (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3 H, t, *J* = 6.9 Hz, 8′-Me), 0.94 (3 H, d, *J* = 6.7 Hz, C$_{4'}$-Me), 1.14–1.34 (6 H, m, (C*H*$_2$)$_3$CH$_3$), 1.32 (3 H, s, *Me*COBn), 1.55–1.88 (4 H, m, 3-H_2, 4-H_2), 2.20 (1 H, dt, *J* = 9.9, 7.0 Hz, part of 5-H_2), 2.58 (1 H, m, 4′-H), 2.91–2.94 (2 H, m, 2-H, part of 5-H_2), 3.16 (1 H, d, *J* = 13.7 Hz, 1′-H), 3.43 (1 H, dd, *J* = 13.7, 1.7 Hz, 1′-H), 3.54 (3 H, s, OMe), 3.57 (3 H, s, OMe), 4.67 (1 H, s, C*H*$(OMe)_2$), 4.72 and 4.85 (1 H, AB q, *J* = 11.5 Hz, C*H*$_2$Ph), 6.05 (1 H, br d, *J* = 10.3 Hz, 3′-H), 7.19–7.41 (5 H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.7, 20.5, 22.8, 24.1, 27.3, 29.5, 36.6, 36.8, 53.1, 56.9, 58.4, 61.1, 66.1, 68.5, 82.8, 103.9, 109.6, 126.8, 127.4 (2 carbons), 128.1 (2 carbons), 140.4, 148.7.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-formylethyl]-*N*-[(*E*)-(*R*)-2-iodo-4-methyl-2-octenyl]pyrrolidine (56). To a cold (−78 °C), stirred solution of **55** (205 mg, 0.387 mmol) in CH_2Cl_2 (8 mL) was added dropwise Me_2BBr (3.9 mL of a 1.0 M solution in CH_2Cl_2, 3.9 mmol), and the mixture was stirred at −78 °C. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and CH_2Cl_2 (10 mL) was added to the mixture. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and column chromatography on silica gel (hexane–EtOAc, 4:1) gave **56** (125 mg, 67%) as a pale yellow oil: IR (neat) 1729, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 6.9 Hz, 8′-Me), 0.94 (3 H, d, *J* = 6.6 Hz, C$_{4'}$-Me), 1.12–1.33 (6 H, m, (C*H*$_2$)$_3$Me), 1.51 (3 H, s, *Me*COBn), 1.64–1.87 (4 H, m, 3-H_2, 4-H_2), 2.12–2.20 (1 H, m, part of 5-H_2), 2.58 (1 H, m, 4′-H), 3.01–3.15 (2 H, m, 2-H, part of 5-H_2), 3.23 (1 H, d, *J* = 13.7 Hz, part of 1′-H_2), 3.63 (1 H, dd, *J* = 13.5, 1.7 Hz, part of 1′-H_2), 4.36 and 4.60 (2 H, AB q, *J* = 11.2 Hz, C*H*$_2$Ph), 6.06 (1 H, dd, *J* = 10.3, 1.0 Hz, 3′-H), 7.23–7.42 (5 H, m, Ph), 9.76 (1 H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.5, 20.7, 22.8, 24.3, 26.9, 29.5, 36.5, 36.7, 53.8, 61.0, 66.9, 67.3, 86.8, 101.9, 127.5 (2 carbons), 127.6, 128.4 (2 carbons), 138.6, 149.2, 205.4.

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-[(*E*)-(*R*)-2-methylhexylidene]octahydroindolizine (58). A. Cyclization with Nickel(II) Chloride as a Catalyst. To a stirred mixture of $CrCl_2$ (298 mg, 2.42 mmol), $NiCl_2$ (1.5 mg, 0.012 mmol), and DMF (3 mL) under Ar was added a solution of **56** (234 mg, 0.485 mmol) in DMF (2 mL), and the mixture was stirred at room temperature for 20 h. After addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with EtOAc (3 × 20 mL), and the extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) afforded a white solid, which was recrystallized from Et_2O–hexane to give **58** (92 mg, 53%) as colorless fine needles: mp 126–127 °C; $[\alpha]^{28}_D$ +15.8° (*c* 0.41, $CHCl_3$); IR (neat) 3406, 2880, 2871, 2800, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 7.1 Hz, 15-Me), 0.99 (3 H, d, *J* = 6.5 Hz, C$_{11}$-Me), 1.25 (3 H, s, C$_9$-Me), 1.12–1.37 (6 H, m, (C*H*$_2$)$_3$Me), 1.62–2.03 (4 H, m, 1-H_2, 2-H_2), 2.15 (1 H, m, 3-H_{ax}), 2.42–2.47 (2 H, m, 8a-H, 11-H), 2.75 (1 H, d, *J* = 12.4 Hz, 5-H_{ax}), 3.12 (1 H, t, *J* = 8.3 Hz, 3-H_{eq}), 3.70 (1 H, d, *J* = 12.4 Hz, 5-H_{eq}), 4.06 (1 H, s, 7-H), 4.57 and 4.58 (2 H, AB q, *J* = 12.7 Hz, C*H*$_2$Ph), 5.25 (1 H, d, *J* = 9.5 Hz, 10-H), 7.17–7.32 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.8, 20.95, 21.01, 22.8, 22.9, 29.6, 31.8, 37.4, 48.7, 54.5, 64.6, 66.6, 76.3, 76.5, 126.9, 127.2 (2 carbons), 128.1 (2 carbons), 134.1, 136.6, 140.4; CIMS (isobutane) *m/z* 358 (MH^+), 340, 266; EIMS *m/z* (relative intensity) 358 (M^+ + 1, 0.4), 340 (M^+ − OH, 0.4), 266 (M^+ − Bn, 72), 234 (5), 137 (3), 108 (3), 83 (100), 65 (7); HRMS calcd for $C_{16}H_{28}NO_2$ (M^+ − Bn) 266.210, found 266.2103. Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.23; H, 9.88; N, 3.97.

B. Cyclization with Nickel(II) Acetylacetonate as a Catalyst. To a stirred mixture of $CrCl_2$ (95 mg, 0.77 mmol), Ni(acac)$_2$ (1.0 mg, 0.0039 mmol), and DMF (1 mL) under Ar was added a solution of **56** (75 mg, 0.16 mmol) in DMF (2 mL), and the mixture was stirred at room temperature for 20 h. A workup similar to that described above afforded a residue, which was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) to give **58** (17 mg, 31%).

(+)-Allopumiliotoxin 267A (1). A solution of **58** (50 mg, 0.14 mmol) in THF (2 mL) was added dropwise to liquid NH_3 (5 mL) at −78 °C with stirring. To this mixture was added Li (8 mg, 1.2 mmol) in small portions, the cooling bath was removed, and the mixture was stirred for 30 min. The resulting purple-blue mixture was quenched by addition of NH_4Cl and allowed to warm to room temperature to evaporate the ammonia. To the residue was added saturated aqueous $NaHCO_3$ (5 mL), the mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) to give an oil which was solidified with time on cooling to provide **1** (34 mg, 90%) as a colorless solid: mp 45–47 °C; $[\alpha]^{25}_D$ +24.1° (*c* 1.1, MeOH) (lit.[2b] $[\alpha]^{25}_D$ +24.7° (*c* 0.17, MeOH), lit.[3b] $[\alpha]^{25}_D$ +31° (*c* 0.22, MeOH)); IR (neat) 3419, 2873, 2856, 2796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 7.2 Hz, 15-Me), 0.98 (3 H, d, *J* = 6.6 Hz, C$_{11}$-Me), 1.21 (3 H, s, 9-Me), 1.13–1.38 (6 H, m, (C*H*$_2$)$_3$Me), 1.65–1.77 (4 H, m, 1-H_2, 2-H_2), 2.27 (1 H, m, 3-H_{ax}), 2.39 (1 H, m, 11-H), 2.49 (1 H, m, 8a-H), 2.73 (1 H, br d, *J* = 12.1 Hz, 5-H_{ax}), 2.92 (1 H, br s, OH), 3.05 (1 H, m, 3-H_{eq}), 3.61 (1 H, d, *J* = 12.1 Hz, 5-H_{eq}), 3.72 (1 H, s, 7-H), 5.34 (1 H, dd, *J* = 9.7, 1.1 Hz, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.7, 21.28, 21.33, 21.3, 22.7, 22.8, 29.7, 32.0, 37.1, 48.9, 54.3, 65.3, 70.4, 80.9, 133.2, 138.9; EIMS *m/z* (relative intensity) 267 (M^+, 7), 250 (M^+ − OH, 20), 234 (4), 222 (5), 206 (5), 182 (15), 164 (4), 150 (5), 114 (20), 83 (100), 70 (9); HRMS calcd for $C_{16}H_{29}NO_2$ (M^+) 267.2198, found 267.2182.

(2*RS*,3*R*,4*R*)-3,4-(Isopropylidenedioxy)-2-pentanol (60). To an ice-cold, stirred solution of **59** (6.33 g, 43.9 mmol) in THF (60 mL) was added dropwise MeMgBr (65.5 mL of a 2.01 M solution in THF, 132 mmol) under Ar. After the mixture was stirred in an ice bath for 1 h, water (20 mL) was added to the mixture, and the slurry that formed was separated by decantation and washed with Et_2O (2 × 25 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **60** (6.12 g, 87%) as a colorless oil, which was identified as a 6:1 mixture of the diastereomers by ^1H NMR: $[\alpha]^{27}_D$ −14.7° (*c* 2.0, $CHCl_3$); IR (neat) 3446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 and 1.20 (total 3 H with 6:1 ratio, d, *J* = 6.6 Hz, 1-Me each), 1.24 and 1.32 (total 3 H with 1:6 ratio, d, *J* = 6.0 Hz, 5-Me each), 1.38 (3 H, s, acetonide Me), 1.40 (3 H, s, acetonide me), 2.18 (1 H, br s, OH), 3.40

and 3.49 (total 1 H with 1:6 ratio, dd, J = 8.0, 4.8 Hz and 8.0, 4.2 Hz, respectively, 3-H each), 3.62–3.74 and 3.9–3.99 (total 1 H with 1:6 ratio, m, 2-H each), 4.08 (1 H, dq, J = 8.0, 6.0 Hz, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 18.5, 19.6, 26.9, 27.4, 66.7, 72.7, 85.7, 108.1; CIMS (isobutane) m/z 161 (MH^+), 145; EIMS m/z (relative intensity), 145 (M^+ – Me, 86), 131 (24), 115 (100), 99 (26), 85 (78), 61 (20); HRMS calcd for $C_7H_{13}O_3$ (M^+ – Me) 145.0865, found 145.0882.

(3*S*,4*R*)-3,4-(Isopropylidenedioxy)-2-propanone (61). A solution of **60** (3.54 g, 22.1 mmol) in CH_2Cl_2 (30 mL) was added to a stirred suspension, which was obtained by addition of silica gel (7 g) to a solution of PCC (7.15 g, 33.2 mmol) in CH_2Cl_2 (75 mL) at room temperature, and the resulting mixture was stirred at room temperature. After being stirred for 20 h, the mixture was filtered and washed with Et_2O (50 mL). The combined filtrates were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (hexane–EtOAc, 10:1) afforded **61** (2.94 g, 84%) as a colorless oil: $[\alpha]^{28}_D$ –66.0° (c 0.62, $CHCl_3$); IR (neat) 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (3 H, d, J = 6.0 Hz, 5-Me), 1.43 (3 H, s, acetonide Me), 1.44 (3 H, s, acetonide Me), 2.25 (3 H, s, 1-Me), 3.86 (1 H, d, J = 8.3 Hz, 3-H), 4.02 (1 H, dq, J = 8.3, 6.0 Hz, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 26.3, 26.4, 27.2, 74.1, 86.8, 110.1, 208.3; CIMS (isobutane) m/z 159 (MH^+), 143, 115, 84.

Ethyl (*E*)-(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-methyl-2-hexenoate (62). To a cold (5 °C), stirred suspension of NaH (60% in mineral oil, 960 mg, 24.0 mmol) in benzene (30 mL) under Ar was added dropwise a solution of diisopropyl (ethoxycarbonyl)methanephosphonate (6.05 g, 24.0 mmol) in benzene (20 mL). The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was recooled to 5 °C, and to this was added dropwise a solultion of **61** (2.53 g, 16.0 mmol) in benzene (10 mL) over a period of 5 min. The cooling bath was removed, and the mixture was stirred for another 2 h. After addition of water (20 mL), the mixture was extracted with benzene (3 × 40 mL), and the combined extracts were washed with brine (40 mL) and dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel (hexane–EtOAc, 50:1) gave **62** (3.06 g, 84%) as a colorless oil: $[\alpha]^{30}_D$ –3.65° (c 1.2, $CHCl_3$); IR (neat) 1719, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3 H, d, J = 7.1 Hz, CO_2CH_2*Me*), 1.31 (3 H, d, J = 5.9 Hz, 6-Me), 1.43 (6 H, s, acetonide 2 × Me), 2.15 (3 H, d, J = 1.3 Hz, C_3-Me), 3.85 (1 H, dq, J = 8.3, 5.9 Hz, 5-H), 3.94 (1 H, br d, J = 8.3 Hz, 4-H), 4.16 (2 H, q, J = 7.2 Hz, CO_2C*H*$_2$Me), 5.96 (1 H, m, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.6, 17.8, 26.6, 27.4, 59.9, 76.0, 86.9, 109.0, 117.3, 153.9, 166.4; EIMS m/z (relative intensity) 213 (M^+ – Me, 17), 184 (5), 139 (4), 126 (70), 111 (18), 98 (100), 83 (96), 69 (10); HRMS calcd for $C_{11}H_{17}O_4$ (M^+ – Me) 213.1127, found 213.1115.

(*E*)-(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-methyl-2-hexen-1-ol (63). To a cold (–78 °C), stirred solution of **62** (2.56 g, 11.2 mmol) in CH_2Cl_2–hexane (2:1, 45 mL) was added dropwise DIBALH (48.2 mL of a 0.93 M solution in hexane, 44.8 mmol) under Ar. The mixture was stirred at the same temperature for 30 min and quenched by MeOH (1 mL). After the mixture was warmed to room temperature, saturated aqueous NH_4Cl (2 mL) and then Et_2O (300 mL) were added to the mixture. The mixture was filtered through a Celite pad, and the filtrate was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by silica gel chromatography (hexane–EtOAc, 10:1) gave **63** (2.03 g, 97%) as a colorless oil: $[\alpha]^{30}_D$ –8.66° (c 1.1, $CHCl_3$); IR (neat) 3419, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3 H, d, J = 5.6 Hz, 6-Me), 1.42 (6 H, s, acetonide 2 × Me), 1.67 (1 H, br s, OH), 1.69 (3 H, br s, C_3-Me), 3.82–3.85 (2 H, m, 4-H, 5-H), 4.22 (2 H, m, 1-H_2), 5.73 (1 H, br t, J = 6.4 Hz, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 17.2, 26.9, 27.5, 59.2, 74.8, 87.7, 108.3, 128.3, 134.4; EIMS m/z (relative intensity) 171 (M^+ – Me, 11), 142 (10), 111 (68), 93 (6), 84 (100), 71 (16); HRMS calcd for $C_9H_{15}O_3$ (M^+ – Me) 171.1021, found 171.1027.

(*E*)-(4*R*,5*R*)-1-Bromo-4,5-(isopropylidenedioxy)-3-methyl-2-hexene (64). To an ice-cold, stirred mixture of **63** (2.32 g, 12.5 mmol), triphenylphosphine (6.53 g, 24.9 mmol), and CH_2Cl_2 (30 mL) was added CBr_4 (8.26 g, 24.9 mmol). After 5 min, the mixture was concentrated in vacuo, and Et_2O (100 mL) was added to the residue. The crystalline material of $Ph_3P(O)$ that separated was removed by filtration, and the filtrate was concentrated to give a pale yellow oil, which was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **64** (2.92 g, 94%) as a colorless oil: $[\alpha]^{30}_D$ –12.3° (c 1.6, $CHCl_3$); IR (neat) 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3 H, d, J = 5.8 Hz, 6-Me), 1.42 (6 H, s, acetonide 2 × Me), 1.75 (3 H, d, J = 1.1 Hz, C_3-Me), 3.84 (1 H, dq, J = 8.5, 5.8 Hz, 5-H), 3.90 (1 H, d, J = 8.5 Hz, 4-H), 4.00 (2 H, d, J = 8.4 Hz, 1-H_2), 5.86 (1 H, br t, J = 8.4 Hz, 2-H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 11.6, 17.3, 26.8, 27.4, 27.5, 75.0, 87.2, 108.5, 124.3, 138.4; EIMS m/z (relative intensity) 235 (M^+ + 2 – Me, 5), 233 (M^+ – Me, 5), 206 (4), 203 (4), 193 (2), 191 (2), 165 (1), 163 (1), 148 (2), 146 (3), 125 (100), 111 (20), 95 (4), 84 (33), 67 (39); HRMS calcd for $C_9H_{14}O_2{}^{79}Br$ (M^+ – Me) 233.0177, found 233.0172.

(4*S*)-4-Isopropyl-3-[(*E*)-(2*R*,6*R*,7*R*)-6,7-(isopropylidenedioxy)-2,5-dimethyl-4-octenoyl]-2-oxazolidinone (66). To a cold (–78 °C), stirred solution of LDA, prepared from a solution of (i-Pr)$_2$NH (1.66 g, 16.4 mmol) in THF (19 mL) and BuLi (9.9 mL of 1.66 M solution in hexane, 16.4 mmol), was added (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone (2.76 g, 14.9 mmol) under Ar. After 30 min, a solution of **64** (4.08 g, 16.4 mmol) in THF (8 mL) was added dropwise at –78 °C with stirring, and the resulting mixture was stirred at the same temperature for 15 h and then at 0 °C for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic phases were washed successively with 1 M $NaHSO_3$, 1 M $KHCO_3$, and brine. The oily residue obtained by drying ($MgSO_4$) and concentration was purified by chromatography on silica gel (hexane–EtOAc, 20:1) to give **66** (4.37 g, 83%) as a colorless oil: $[\alpha]^{26}_D$ +38.7° (c 2.1, $CHCl_3$); IR (neat) 1780, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 6.9 Hz, isopropyl Me), 0.91 (3 H, d, J = 7.0 Hz, isopropyl Me), 1.13 (3 H, d, J = 6.8 Hz, $C_{2'}$-Me), 1.20 (3 H, d, J = 5.6 Hz, 8′-Me), 1.40 (3 H, acetonide Me), 1.41 (3 H, s, acetonide Me), 1.67 (3 H, s, $C_{5'}$-Me), 2.25 (1 H, m, part of 3′-H_2), 2.32 (1 H, m, 2′-H), 2.51 (1 H, m, part of 3′-H_2), 3.79–3.89 (2 H, m, 6′-H, 7′-H), 4.19 (1 H, dd, J = 9.1, 3.4 Hz, part of 5-H_2), 4.25 (1 H, t, J = 8.5 Hz, part of 5-H_2), 4.45 (1 H, dt, J = 8.5, 3.4 Hz, 4-H), 5.51 (1 H, br t, J = 7.3 Hz, 4′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 14.8, 16.2, 17.1, 18.0, 26.9, 27.5, 28.5, 32.2, 37.6, 58.6, 63.3, 74.6, 88.4, 108.0, 126.2, 133.6, 153.8, 176.6; CIMS (isobutane) m/z 353 (M^+), 338; EIMS m/z (relative intensity) 338 (M^+ – Me, 3), 309 (M^+ – 44, 6), 278 (3), 252 (0.4), 212 (1.7), 185 (45), 167 (4) 149 (28), 124 (100), 107 (5), 86 (93), 67 (18); HRMS calcd for $C_{18}H_{28}NO_5$ (M^+ – Me) 338.1968, found 338.1960. Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.57; H, 8.84; N, 3.96. Found: C, 64.41; H, 8.82; N, 3.97.

(*E*)-(2*R*,6*R*,7*R*)-6,7-(Isopropylidenedioxy)-2,5-dimethyl-4-octen-1-ol (67). To an ice-cold, stirred slurry of $LiAlH_4$ (908 mg, 23.9 mmol) in THF (30 mL) was added dropwise a solution of **66** (2.82 g, 7.98 mmol) in THF (25 mL). After being stirred in the ice bath for 1 h, the mixture was quenched with water (1 mL) and then 10% KOH (4 mL) and filtered through a Celite pad. The filtrate was dried ($MgSO_4$) and concentrated to leave an oil, which was purified by silica gel chromatography (hexane–EtOAc, 10:1) to give **67** (1.64 g, 90%) as a colorless oil: $[\alpha]^{28}_D$ +1.22° (c 1.2, $CHCl_3$); IR (neat) 3436, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 6.7 Hz, C_2-Me), 1.21 (3 H, d, J = 5.5 Hz, 8-Me), 1.42 (6 H, s, acetonide 2 × Me), 1.66 (3 H, s, C_5-Me), 1.72 (1 H, m, 2-H), 1.93 (1 H, m, part of 3-H_2), 2.19 (1 H, m, part of 3-H_2), 2.29 (1 H, br s, OH), 3.46 (1 H, dd, J = 10.5, 6.2 Hz, part of 1-H_2), 3.50 (1 H, dd, J = 10.5, 6.0 Hz, part of 1-H_2), 3.82–3.89 (2 H, m, 6-H, 7-H), 5.54 (1 H, br t, J = 7.3, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 16.5, 17.1, 27.0, 27.5, 31.5, 36.3, 67.9, 74.4, 88.8, 108.0, 128.2, 132.2; EIMS m/z (relative intensity) 226 (M^+ – 2, 3), 184 (18), 153 (25), 130 (38), 111 (100), 86 (86), 69 (30).

(*E*)-(2*R*,6*R*,7*R*)-6,7-(Isopropylidenedioxy)-2,5-dimethyl-4-octenal (68). To a cold (–78 °C), stirred solution of oxalyl chloride (1.85 g, 14.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of DMSO (2.26 g, 28.9 mmol) in CH_2Cl_2 (20 mL) over a period of 5 min. After the mixture was at –78 °C for 1 h, a solution of **67** (1.65 g, 7.23 mmol) in CH_2Cl_2 (10 mL) was added to the mixture with stirring over period of 5 min, and stirring was continued at –78 °C. After 2 h, Et_3N (4.39 g, 43.4 mmol) was added to the mixture, and the resulting mixture was warmed to room temperature. After addition of water (30 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and then brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **68** (1.52 g, 93%) as a colorless oil: $[\alpha]^{24}_D$ –7.02° (c 1.1, $CHCl_3$); IR (neat) 1729, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3 H, d, J = 7.0 Hz, C_2-Me), 1.21 (3 H, d, J = 5.5 Hz, 8-Me), 1.41 (6 H, s, acetonide 2 × Me), 1.67 (3 H, d, J = 0.9 Hz, C_5-Me), 2.18 (1 H, m, part of 3-H_2), 2.37–2.49 (4 H, m, C_2-Me, part of 3-H_2), 3.80–3.88 (2 H, m, 6-H, 7-H), 5.49 (1 H, br t, J = 6.9 Hz, 4-H), 9.65 (1 H, d, J = 1.4 Hz, CHO); ^{13}C NMR (100 Hz, $CDCl_3$) δ 11.8, 13.1, 17.1, 26.9, 27.5, 28.7, 46.4, 74.6, 88.3, 108.1, 125.8, 133.8, 204.3.

(5*E*)-(3*R*,7*R*,8*R*)-1,1-Dibromo-7,8-(isopropylidenedioxy)-3,6-dimethyl-1,5-nonadiene (69). To a cold (0 °C), stirred solution of **68** (641 mg, 2.83 mmol) and triphenylphosphine (2.97 g, 11.3 mmol) in CH_2Cl_2 (25 mL) was added CBr_4 (1.88 g, 5.67 mmol) in small portions. After being stirred at 0 °C for 5 min, the mixture was washed with saturated aqueous $NaHCO_3$ and then water, dried ($MgSO_4$), and concentrated. Et_2O (50 mL) was added to the residue to separate insoluble $Ph_3P(O)$, which was removed by filtration. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (hexane–EtOAc, 100:1) to give **69** (1.52 g, 908 mg, 84%) as a colorless oil: $[\alpha]^{26}_D$ –1.29° (*c* 0.77, $CHCl_3$); IR (neat) 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3 H, d, *J* = 6.8 Hz, C_3-Me), 1.24 (3 H, d, *J* = 5.6 Hz, 9-Me), 1.43 (6 H, s, acetonide 2 × Me), 1.66 (3 H, t, *J* = 0.6 Hz, 6-Me), 2.12 (2 H, br t, *J* = 7.1 Hz, 4-H_2), 2.55 (1 H, m, 3-H), 3.82–3.90 (2 H, m, 7-H, 8-H), 5.49 (1 H, td, *J* = 7.3, 0.9 Hz, 5-H), 6.20 (1 H, d, *J* = 9.4 Hz, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.2, 18.7, 27.0, 27.6, 33.8, 38.5, 74.7, 87.9, 88.4, 108.1, 126.4, 133.3, 143.5; EIMS *m/z* (relative intensity) 367 (M^+ + 2 – Me, 5), 338 (12), 280 (7), 255 (1.5), 238 (2), 213 (32), 172 (3), 151 (42), 125 (99), 107 (27), 86 (100), 67 (60). Anal. Calcd for $C_{14}H_{22}O_2Br_2$: C, 44.00; H, 5.80. Found: C, 44.02; H, 5.75.

(*E*)-(4*R*,8*R*,9*R*)-8,9-(Isopropylidenedioxy)-4,7-dimethyl-6-decen-2-yn-1-ol (70). To a cold (–78 °C), stirred solution of **69** (1.53 g, 4.01 mmol) in THF (20 mL) under Ar was added dropwise BuLi (4.83 mL of a 1.66 M solution in hexane, 8.02 mmol). After the mixture was stirred at –78 °C for 1 h, a suspension of paraformaldehyde (241 mg, 8.03 mmol as HCHO) in THF (4 mL) was added to the mixture over a period of 5 min with stirring. The mixture was stirred for another 10 min at –78 °C and then for 45 min, during the period of which the mixture was allowed to warm to room temperature. After the reaction was quenched with water (10 mL), the mixture was diluted with Et_2O (150 mL), and the organic phase was separated, washed with brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by chromatography on silica gel (hexane–EtOAc, 10:1) gave **70** (930 mg, 92%) as a colorless oil: $[\alpha]^{25}_D$ –12.2° (*c* 1.2, $CHCl_3$); IR (neat) 3436, 2249, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3 H, d, *J* = 6.9 Hz, C_4-Me), 1.23 (3 H, d, *J* = 5.5 Hz, 10-Me), 1.42 (6 H, s, acetonide 2 × Me), 1.67 (3 H, d, *J* = 0.5 Hz, C_7-Me), 1.82 (1 H, br s, OH), 2.15–2.30 (2 H, m, 5-H_2), 2.54 (1 H, m, 4-H), 3.83–3.91 (2 H, m, 8-H, 9-H), 4.22 (1 H, d, *J* = 1.9 Hz, 1-H), 4.23 (1 H, d, *J* = 2.0 Hz, 1-H), 5.57 (1 H, br t, *J* = 7.3 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.1, 20.4, 26.1, 26.9, 27.6, 34.8, 51.3, 74.5, 79.0, 88.7, 90.2, 108.1, 127.3, 132.9; CIMS (isobutane) *m/z* 251 (MH^+), 237, 208; EIMS *m/z* (relative intensity) 237 (M^+ – Me, 10), 208 (13), 193 (8), 177 (6), 165 (4), 150 (9), 136 (5), 125 (42), 107 (30), 86 (100), 67 (42); HRMS calcd for $C_{14}H_{21}O_3$ (M^+ – Me) 237.1491, found 237.1484.

(2*E*,6*E*)-(4*R*,8*R*,9*R*)-8,9-(Isopropylidenedioxy)-4,7-dimethyl-2-(tributylstannyl)-2,6-decadien-1-ol (71). To a stirred solution of **70** (648 mg, 2.57 mmol) in THF (10 mL) under Ar was added $PdCl_2(PPh_3)_2$ (36 mg, 0.051 mmol) at room temperature. After the resulting mixture was stirred for 10 min, *t*-Bu_3SnH (822 mg, 2.82 mmol) was added dropwise to the mixture over 5 min and stirring was continued for 10 min. The mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (hexane–EtOAc, 20:1). The first fraction afforded **71** (1.30 g, 93%) as a colorless oil: $[\alpha]^{26}_D$ –30.5° (*c* 1.4, $CHCl_3$); IR (neat) 3490, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87–0.92 (15 H, m), 0.98 (3 H, d, *J* = 6.6 Hz, C_4-Me), 1.21 (3 H, d, *J* = 5.7 Hz, 10-Me), 1.27–1.36 (6 H, m), 1.41 (6 H, s, acetonide 2 × Me), 1.46–1.54 (6 H, m), 1.62 (3 H, d, *J* = 1.0 Hz, C_7-Me), 1.76 (1 H, dd, *J* = 7.1, 4.7 Hz, OH), 1.93–2.07 (2 H, m, 5-H_2), 2.52 (1 H, m, 4-H), 3.84–3.90 (2 H, m, 8-H, 9-H), 4.20 (1 H, ddd, *J* = 12.9, 7.1, 1.9 Hz, J_{Sn-H} = 23.3 Hz, 1-H), 4.37 (1 H, ddd, *J* = 12.9, 4.7, 1.8 Hz, J_{Sn-H} = 26.2 Hz, 1-H), 5.29 (1 H, dt, *J* = 9.4, 2.1 Hz, J_{Sn-H} = 35.0 Hz, 3-H), 5.52 (1 H, dt, *J* = 7.6, 1.2 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (3 carbons), 11.9, 13.8 (3 carbons) 17.1, 21.0, 27.0, 27.4, 27.5 (3 carbons), 29.3 (3 carbons), 34.0, 35.4, 63.6, 74.4, 88.8, 108.0, 128.9, 131.6, 144.4, 145.2; EIMS *m/z* (relative intensity) 487 (M^+ – Bu, 25), 410 (27), 355 (5), 291 (16), 251 (100), 177 (37), 137 (40), 105 (8); HRMS calcd for $C_{23}H_{43}O_3{}^{120}Sn$ (M^+ – Bn) 487.2234, found 487.2213.

The second fraction afforded (2*E*,6*E*)-(4*R*,8*R*,9*R*)-8,9-(isopropylidenedioxy)-4,7-dimethyl-3-(tributylstannyl)-2,6-decadien-1-ol (**72**) (53 mg, 3.8%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.87–0.94 (15 H, m), 0.97 (3 H, d, *J* = 6.7 Hz, C_4-Me), 1.23 (3 H, d, *J* = 5.4 Hz, 10-Me), 1.28–1.37 (6 H, m), 1.42 (6 H, s, acetonide 2 × Me), 1.44–1.54 (6 H, m), 1.64 (3 H, s, C_7-Me), 1.91 (1 H, quint, *J* = 7.2 Hz, part of 5-H_2), 2.04 (1 H, quint, *J* = 7.2 Hz, part of 5-H_2), 2.81 (1 H, m, 4-H), 3.85 (2 H, m, 8-H, 9-H), 4.13 (1 H, m, 1-H), 4.24 (1 H, m, 1-H), 5.49 (1 H, br t, *J* = 7.4 Hz, 6-H), 5.69 (1 H, t, *J* = 6.2 Hz, J_{Sn-H} = 35.1 Hz, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (3 carbons), 12.3, 13.7 (3 carbons), 17.2, 21.8, 26.9, 27.5 (4 carbons), 29.2 (3 carbons), 35.7, 37.5, 59.5, 74.8, 88.4, 108.0, 128.5, 131.7, 138.5, 153.6.

(2*E*,6*E*)-(4*R*,8*R*,9*R*)-2-Iodo-8,9-(isopropylidenedioxy)-4,7-dimethyl-2,6-decadien-1-ol (73). To a cold (–78 °C), stirred solution of **71** (1.05 g, 1.93 mmol) in CH_2Cl_2 (10 mL) was added a solution of I_2 (589 mg, 2.32 mmol) in CH_2Cl_2 (20 mL) under Ar, and the resulting mixture was stirred at –78 °C for 15 min. After being warmed to room temperature, the mixture was stirred for an additional 30 min, washed with 10% $NaHSO_3$ followed by 10% KF, and dried ($MgSO_4$). Removal of the solvent in vacuo and purification by chromatography on silica gel (hexane–EtOAc, 10:1) gave **73** (721 mg, 98%) as a colorless: $[\alpha]^{28}_D$ –55.2° (*c* 1.4, $CHCl_3$); IR (neat) 3446, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3 H, d, *J* = 6.6 Hz, C_4-Me), 1.22 (3 H, d, *J* = 5.5 Hz, 10-Me), 1.42 (3 H, s, acetonide Me), 1.43 (3 H, s, acetonide Me), 1.64 (3 H, d, *J* = 0.5 Hz, C_7-Me), 1.96–2.09 (2 H, m, 5-H_2), 2.52–2.63 (1 H, m, 4-H), 2.59 (1 H, dd, *J* = 8.8, 4.9 Hz, OH), 3.84–3.92 (2 H, m, 8-H, 9-H), 3.99 (1 H, ddd, *J* = 13.1, 8.8, 0.9 Hz, 1-H), 4.19 (1 H, ddd, *J* = 13.1, 4.9, 0.6 Hz, 1-H), 5.52 (1 H, br t, *J* = 7.7 Hz, 6-H), 6.05 (1 H, d, *J* = 10.2 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 17.1, 20.6, 26.9, 27.5, 34.8, 36.5, 65.0, 74.7, 88.3, 103.6, 108.1, 127.5, 132.9, 147.6; EIMS *m/z* (relative intensity) 380 (M^+, 0.3), 365 (M^+ – Me, 0.9), 336 (15), 304 (6), 209 (4), 177 (4), 151 (22), 125 (77), 105 (8), 86 (100), 67 (43).

(2*E*,6*E*)-(4*R*,8*R*,9*R*)-1-Bromo-2-iodo-8,9-(isopropylidenedioxy)-4,7-dimethyl-2,6-decadiene (74). To an ice-cold, stirred solution of **73** (612 mg, 1.61 mmol) and triphenylphosphine (844 mg, 3.23 mmol) in CH_2Cl_2 (10 mL) was added CBr_4 (1.07 g, 3.22 mmol) under Ar, and the resulting mixture was stirred at 0 °C for 5 min. After evaporation of the solvent, Et_2O (50 mL) was added to the residue, and the solid that separated was removed by filtration. The filtrate was condensed, and the residue was purified by chromatography on silica gel (hexane–EtOAc, 50:1) to give **74** (699 mg, 98%) as a colorless oil: $[\alpha]^{30}_D$ –25.2° (*c* 1.1, $CHCl_3$); IR (neat) 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3 H, d, *J* = 6.7 Hz, C_4-Me), 1.23 (3 H, d, *J* = 5.6 Hz, 10-Me), 1.42 (6 H, s, acetonide 2 × Me), 1.66 (3 H, d, *J* = 0.5 Hz, C_4-Me), 2.10 (2 H, t, *J* = 7.3 Hz, 5-H_2), 2.51–2.62 (1 H, m, 4-H), 3.81–3.89 (2 H, m, 8-H, 9-H), 4.26 and 4.27 (2 H, AB q, *J* = 11.1 Hz, 1-H_2), 5.48 (1 H, dt, *J* = 7.3, 0.9 Hz, 6-H), 6.15 (1 H, d, *J* = 10.3 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.2, 19.5, 27.0, 27.5, 34.3, 36.4, 37.3, 74.6, 88.3, 93.6, 108.1, 126.3, 133.4, 151.9; CIMS (isobutane) *m/z* 444 (M^+ + 2), 442 (M^+); EIMS *m/z* (relative intensity) 429 (M^+ + 2 – Me, 5), 427 (M^+ – Me, 5), 400 (9), 398 (10), 319 (25), 261 (22), 219 (4), 191 (12), 148 (16), 12 5 (100), 105 (20); HRMS calcd for $C_{14}H_{21}O_2{}^{79}BrI$ (M^+ – Me) 426.9770, found 426.9768.

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-[(*R*)-1-(benzyloxy)-1-(dimethoxymethyl)ethyl]pyrrolidine (75). To an ice-cold, stirred solution of **54** (546 mg, 1.95 mmol) and Et_3N (257 mg, 2.54 mmol) in CH_2Cl_2 (10 mL) was added using a microsyringe benzyl chloroformate (433 mg, 2.54 mmol), and the resulting mixture was stirred at room temperature. After 30 min, the mixture was diluted with CH_2Cl_2 (50 mL), washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue on silica gel (hexane–EtOAc, 9:1) gave **75** (638 mg, 79%) as a colorless oil: $[\alpha]^{26}_D$ –71.1° (*c* 1.7, $CHCl_3$); IR (neat) 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (3 H, s, *Me*COBn), 1.66–2.07 (2 H, m, 3-H_2, 4-H_2), 3.31–3.37 (1 H, m, part of 5-H_2), 3.42 (3 H, s, OMe), 3.50 (3 H, s, OMe), 3.74 (1 H, br s, part of 5-H_2), 4.25 (1 H, s, C*H*(OMe)$_2$), 4.28 (1 H, dd, *J* = 8.1, 2.5 Hz, 2-H), 4.59 and 4.76 (2 H, AB q, *J* = 11.6 Hz, C_2-COCH_2Ph), 5.12 and 5.20 (2 H, br AB q, *J* = 12.4 Hz, CO_2CH_2Ph), 7.22–7.39 (10 H, m, 2 × Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.4, 26.3, 47.8, 56.6, 59.6, 62.6, 66.1, 66.8, 82.0, 109.8, 127.0 (4 carbons), 127.7, 127.8, 128.2 (2 carbons), 128.4 (2 carbons), 137.2, 140.1, 156.2; EIMS *m/z* (relative intensity) 382 (M^+ – OMe, 0.8), 338 (M^+ – CH(OMe)$_2$, 1), 294 (2), 275 (2), 246 (0.8), 204 (56), 178 (14), 160 (100), 135 (8), 109 (13). Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.51; H, 7.51; N, 3.45.

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-[(*R*)-1-(benzyloxy)-1-formylethyl]-pyrrolidine (76). To a solution of **75** (572 mg, 1.38 mmol) in THF (8 mL) was added 3 N HCl (8 mL), and the resulting mixture was stirred at room temperature. After 30 min, the mixture was basified with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography on silica gel (hexane–EtOAc, 4:1) gave **76** (503 mg, 99%) as a colorless oil: IR (neat) 1733, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (3 H, br

s, *Me*COBn), 1.63–2.23 (4 H, m, 3-H_2, 4-H_2), 3.40 (1 H, m, part of 5-H_2), 3.63 (1 H, br s, part of 5-H_2), 4.12 (1 H, br s, 2-H), 4.46 (1 H, br s, C_2-COC*H*Ph), 4.48 (1 H, br s, C_2-COC*H*Ph), 5.13 (2 H, br s, CO_2CH_2Ph), 7.26–7.36 (10 H, m, 2 × Ph), 9.67 (1 H, br s, CHO); EIMS *m/z* (relative intensity) 368 (M^+ + 1, 0.4), 338 (M^+ – CHO, 0.6), 294 (2), 248 (5), 204 (73), 181 (9), 160 (100), 140 (6), 109 (10); HRMS calcd for $C_{21}H_{24}NO_3$ (M^+ – CHO) 338.1756, found 338.1755.

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-[(*R*)-1-(benzyloxy)-1-(hydroxymethyl)ethyl]pyrrolidine (77). To a stirred solution of **76** (475 mg, 1.29 mmol) in MeOH (8 mL) was added $NaBH_4$ (245 mg, 6.48 mmol) in small portions at room temperature, and the mixture was stirred for 1 h. The resulting mixture was cooled in an ice bath, neutralized with 1 N HCl, and extracted with $CHCl_3$ (3 × 30 mL). The extracts were washed with saturated aqueous $NaHCO_3$ followed by brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 5:1) to give **77** (468 mg, 98%) as colorless crystals, a part of which was recrystallized from Et_2O–hexane to give colorless needles: mp 76–77 °C; $[\alpha]^{26}_D$ –86.4° (*c* 1.0, $CHCl_3$); IR (neat) 3416, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (3 H, s, *Me*COBn), 1.66–2.20 (4 H, m, 3-H_2, 4-H_2), 3.33 (1 H, m, part of 5-H_2), 3.49–3.63 (2 H, m, CH_2OH), 3.69 (1 H, m, part of 5-H_2), 4.15 (1 H, dd, *J* = 8.5, 2.7 Hz, 2-H), 4.42 and 4.51 (2 H, AB q, *J* = 11.5 Hz, C_2-COCH_2Ph), 4.88 (1 H, dd, *J* = 9.3, 6.0 Hz, OH), 5.17 (2 H, s, CO_2CH_2Ph), 7.24–7.39 (10 H, m, 2 × Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 24.7, 25.9, 47.6, 62.1, 64.5, 64.8, 67.5, 80.5, 126.8 (2 carbons), 127.2 (2 carbons), 127.8, 128.1, 128.2 (2 carbons), 128.5 (2 carbons), 136.5, 139.6, 157.6; EIMS *m/z* (relative intensity) 370 (M^+ + 1, 0.1), 338 (M^+ – CH_2OH, 0.3), 294 (0.5), 248 (3), 204 (23), 160 (30), 91 (100), 65 (13); HRMS calcd for $C_{22}H_{28}NO_4$ (M^+ + 1) 370.2018, found 370.2009. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.26; H, 7.40; N, 3.78.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-[(*tert*-butyldimethylsiloxy)methyl]ethyl]-*N*-[(benzyloxy)carbonyl]pyrrolidine (78). To a stirred solution of **77** (364 mg, 0.986 mmol) in DMF (5 mL) were added imidazole (87 mg, 1.28 mmol), DMAP (12 mg, 0.098 mmol), and *tert*-butylchlorodimethylsilane (193 mg, 1.28 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and column chromatography on silica gel (hexane–EtOAc, 10:1) gave **78** (448 mg, 94%) as a colorless oil: $[\alpha]^{27}_D$ –34.5° (*c* 1.2, $CHCl_3$); IR (neat) 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (6 H, br s, $SiMe_2$), 0.90 (9 H, br s, Si^{t}Bu), 1.29 (3 H, br s, *Me*COBn), 1.68–2.22 (4 H, m, 3-H_2, 4-H_2), 3.33 (1 H, ddd, *J* = 10.8, 8.4, 6.0 Hz, part of 5-H_2), 3.65–3.82 (3 H, m, 2-H, CH_2OSi), 4.11 (1 H, br d, *J* = 6.9 Hz, 2-H), 4.59–4.77 (2 H, AB q, *J* = 11.7 Hz, C_2HCOCH_2Ph), 5.07 (1 H, $^1/_2$ br AB q, *J* = 12.5 Hz, part of CO_2CH_2Ph), 5.19 (1 H, $^1/_2$ AB q, *J* = 12.5 Hz, part of CO_2CH_2Ph), 7.22–7.39 (10 H, m, 2 × Ph); CIMS (isobutane) *m/z* 484 (MH^+), 469, 426; EIMS *m/z* (relative intensity) 468 (M^+ – Me, 0.3), 426 (M^+ – Bu, 5), 382 (0.9), 320 (2), 278 (17), 204 (57), 160 (100), 131 (20); HRMS calcd for $C_{24}H_{32}NO_4Si$ (M^+ – Bu) 426.2101, found 426.2099. Anal. Calcd for $C_{28}H_{41}NO_4Si$: C, 69.53; H, 8.54; N, 2.90. Found: C, 69.15; H, 8.54; N, 2.89.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-[(*tert*-butyldimethylsiloxy)methyl]ethyl]pyrrolidine (79). To a solution of **78** (390 mg, 0.807 mmol) in MeOH (5 mL) was added 10% Pd–C (390 mg), and the resulting suspension was vigorously stirred under 1 atm of H_2 for 5 min. After removal of the catalyst by filtration, the filtrate was concentrated, and the residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 350:9:1) to give **79** (240 mg, 85%) as colorless crystals, a part of which was recrystallized from Et_2O–hexane to give colorless needles: mp 79–80 °C; $[\alpha]^{27}_D$ –13.5° (*c* 0.71, $CHCl_3$); IR (neat) 3475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (3 H, s, $SiMe_2$), 0.10 (3 H, s, SiMe), 0.90 (9 H, s, Si^{t}Bu), 1.24 (3 H, s, *Me*COBn), 1.75–1.97 (4 H, m, 3-H_2, 4-H_2), 2.94–3.03 (1 H, m, part of 5-H_2), 3.08–3.15 (1 H, m, part of 5-H_2), 3.60 (1 H, t, *J* = 7.7 Hz, 2-H), 3.78 and 3.86 (2 H, AB q, *J* = 10.9 Hz, CH_2OSi), 4.54 and 4.57 (2 H, AB q, 11.2 Hz, CH_2Ph), 6.46 (1 H, br s, NH), 7.22–7.35 (5 H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.8, –5.7, 17.2, 18.2, 25.0, 25.8 (3 carbons), 26.2, 46.9, 64.7, 65.4, 67.3, 76.9, 127.2 (2 carbons), 127.3, 128.2 (2 carbons), 138.9; CIMS (isobutane) *m/z* 350 (MH^+); EIMS *m/z* (relative intensity) 334 (M^+ – Me, 0.5), 292 (M^+ – Bu, 3), 243 (0.9), 204 (5), 184 (4), 160 (3), 126 (58), 110 95), 91 (96), 70 (100); HRMS calcd for $C_{19}H_{32}NO_2Si$ (M^+ – Me) 334.2200, found 334.2184. Anal. Calcd for $C_{20}H_{35}NO_2Si$: C, 68.71; H, 10.09; N, 4.01. Found: C, 68.30; H, 9.90; N, 4.13.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-[(*tert*-butyldimethylsiloxy)methyl]ethyl]-*N*-[(2*E*,6*E*)-(4*R*,8*R*,9*R*)-8,9-(isopropylidenedioxy)-4,7-dimethyl-2,6-decadien-1-yl]pyrrolidine (80). A solution of **79** (405 mg, 0.915 mmol), **74** (351 mg, 1.01 mmol), and *i*-Pr_2NEt (177 mg, 1.37 mmol) in THF (5 mL) was stirred under Ar at room temperature for 2 days. The resulting mixture was diluted with Et_2O (50 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 50:1) to give **80** (455 mg, 70%) as a colorless oil: $[\alpha]^{30}_D$ –47.1° (*c* 1.3, $CHCl_3$); IR (neat) 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Si^{t}Bu), 0.94 (3 H, d, *J* = 6.6 Hz, $C_{4'}$-Me), 1.17 (3 H, d, *J* = 5.6 Hz, 10′-Me), 1.27 (3 H, s, *Me*COBn), 1.42 (6 H, s, acetonide 2 × Me), 1.62 (3 H, s, $C_{7'}$-Me), 1.63–1.93 (4 H, m, 3-H_2, 4-H_2), 2.01 (2 H, t, *J* = 7.0 Hz, 5′-H_2), 2.11 (1 H, m, part of 5-H_2), 2.70 (1 H, m, 4′-H), 2.93 (1 H, dd, *J* = 8.9, 5.7, Hz, 2-H), 3.00 (1 H, m, part of 5-H_2), 3.10 (1 H, d, *J* = 13.6 Hz, part of 1′-H_2), 3.64 (1 H, $^1/_2$ AB q, *J* = 10.6 Hz, part of CH_2OSi), 3.69 (1 H, dd, *J* = 13.6, 1.5 Hz, part of 1′-H_2), 3.79–3.86 (2 H, m, 8′-H, 9′-H), 3.89 (1 H, $^1/_2$ AB q, *J* = 10.6 Hz, part of CH_2OSi), 4.64 and 4.70 (2 H, AB q, *J* = 11.6 Hz, CH_2Ph), 5.44 (1 H, td, *J* = 7.3, 1.1 Hz, 6′-H), 6.08 (1 H, d, *J* = 10.0 Hz, 3′-H), 7.20–7.38 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, –5.4, 11.7, 17.1, 17.6, 18.3, 19.7, 24.1, 25.9 (3 carbons), 27.0, 27.45, 27.54, 34.8, 36.3, 54.0, 61.3, 64.8, 66.3, 67.6, 74.5, 81.7, 88.6, 103.8, 108.0, 126.9, 127.1, 127.3 (2 carbons), 128.1 (2 carbons), 132.6, 140.4, 147.7; CIMS (isobutane) *m/z* 712 (MH^+); EIMS *m/z* (relative intensity) 711 (M^+, 2), 695 (8), 653 (2), 565 (2), 478 (2), 432 (100), 373 (8), 304 (5), 262 (10), 189 (3), 136 (32). Anal. Calcd for $C_{35}H_{58}NO_4ISi$: C, 59.06; H, 8.21; N, 1.97. Found: C, 58.83; H, 8.25, N, 1.97.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-*N*-[(2*E*,6*E*)-(4*R*,8*R*,9*R*)-8,9-(isopropylidenedioxy)-4,7-dimethyl-2,6-decadien-1-yl]pyrrolidine (81). A mixture of **80** (412 mg, 0.580 mmol) and tetrabutylammonium fluoride (1.16 mL of a 1.0 M solution in THF, 1.16 mmol) was stirred at room temperature for 16 h. The resulting mixture was diluted with Et_2O (50 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 10:1) to give **81** (325 mg, 94%) as a colorless oil: $[\alpha]^{27}_D$ –49.4° (*c* 1.5, $CHCl_3$); IR (neat) 3436, 1631 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3 H, d, *J* = 6.6 Hz, $C_{4'}$-Me), 1.22 (3 H, d, *J* = 5.6 Hz, 10′-Me), 1.43 (6 H, s, acetonide 2 × Me), 1.45 (3 H, s, *Me*COPh), 1.65 (3 H, s, $C_{7'}$-Me), 1.68–1.85 (1 H, m, 4-H_2), 1.91 (1 H, m, part of 3-H_2), 2.05 (2 H, t, *J* = 7.1 Hz, 5′-H_2), 2.13 (1 H, m, part of 3-H_2), 2.23 (1 H, m, part of 5-H_2), 2.65 (1 H, m, 4′-H), 3.01 (1 H, dd, *J* = 9.4, 3.8 Hz, 2-H), 3.07 (1 H, m, part of 5-H_2), 3.25 (1 H, d, *J* = 13.4 Hz, part of 1′-H_2), 3.38 (1 H, dd, *J* = 13.4, 1.4 Hz, part of 1′-H_2), 3.56 (1 H, d, *J* = 11.2 Hz, part of CH_2OH), 3.82–3.87 (3 H, m, 8′-H, 9′-H, part of CH_2OH), 4.44 and 4.53 (2 H, AB q, *J* = 11.1 Hz, CH_2Ph), 5.46 (1 H, br t, *J* = 7.1, 6′-H), 6.16 (1 H, d, *J* = 10.0 Hz, 3′-H), 7.24–7.33 (5 H, m, Ph); ^{13}C NMR (100 MHz, CD_3OD) δ 12.1, 17.5, 18.9, 20.4, 24.9, 27.3, 27.77, 27.80, 35.8, 37.7, 54.6, 62.8, 65.1, 66.5, 70.8, 75.9, 80.1, 89.7, 102.2, 109.2, 127.7, 128.2 (2 carbons), 128.6 (2 carbons), 129.2, 134.2, 140.9, 150.3; CIMS (isobutane) *m/z* 598 (MH^+); EIMS *m/z* (relative intensity) 598 (M^+ + 1, 10), 582 (M^+ – Me, 10), 432 (100), 374 (11), 346 (4), 290 (3), 263 (11), 136 (40), 105 (8); HRMS calcd for $C_{28}H_{41}NO_4I$ (M^+ – Me) 582.2080, found 582.2103. Anal. Calcd for $C_{29}H_{44}NO_4I$: C, 58.29; H, 7.42; N, 2.34. Found: C, 58.24; H, 7.37; N, 2.45.

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-formylethyl]-*N*-[(2*E*,6*E*)-(4*R*,8*R*,9*R*)-8,9-(isopropylidenedioxy)-4,7-dimethyl-2,6-decadien-1-yl]pyrrolidine (82). To a cold (–78 °C), stirred solution of oxalyl chloride (112 mg, 0.882 mol) in CH_2Cl_2 (3 mL) was added using a syringe DMSO (138 mg, 1.77 mmol), and the resulting mixture was stirred at –78 °C for 1 h. To this mixture was added using a syringe a solution of **81** (264 mg, 0.442 mmol) in CH_2Cl_2 (2 mL) over 5 min at –78 °C. The mixture was stirred at the same temperature for 2 h. Triethylamine (268 mg, 2.65 mmol) was then added, and the resulting mixture was warmed to room temperature. After addition of water (5 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ followed by brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 4:1) to give **82** (226 mg, 86%) as a colorless oil: IR (neat) 1730, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3 H, d, *J* = 6.6 Hz, $C_{4'}$-Me), 1.19 (3 H, d, *J* = 5.7 Hz, 10′-Me), 1.41 (6 H, s, acetonide 2 × Me), 1.49 (3 H, s, *Me*COBn), 1.63 (3 H, s, $C_{7'}$-Me), 1.65–1.94 (4 H, m, 3-H_2, 4-H_2), 2.00–2.18 (3 H, m, part of 5-H_2, 5′-H), 2.67 (1 H, m, 4′-H), 2.95–3.09 (2 H, m, 2-H, part of 5-H_2), 3.23 (1 H, d, *J* = 13.5 Hz, 1′-H), 3.63 (1 H, dd, *J* = 13.5, 1.5 Hz, 1′-H), 3.82–3.91 (2 H, m, 8′-H, 9′-H), 4.35 and 4.59 (2 H, d, AB q, *J* = 11.3 Hz, CH_2Ph), 5.44 (1 H, br t, *J* = 7.3 Hz, 6′-H), 6.11 (1 H,

d, J = 9.2 Hz, 3'-H), 7.28–7.43 (5 H, m, Ph), 9.75 (1 H, s, CHO); CIMS (isobutane) m/z 596 (MH^+); EIMS m/z (relative intensity) 580 (M^+ – Me, 2), 432 (68), 304 (14), 263 (28), 149 (4), 164 (32), 121 (100); HRMS calcd for $C_{28}H_{39}NO_4I$ (M^+ – Me) 580.2078, found 580.2050.

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-6(*Z*)-[6(*R*),7(*R*)-(isopropylidenedioxy)-2(*R*),5-dimethyl-4(*E*)-octenylidene]-8-methyloctahydroindolizine (83). A suspension of $CrCl_2$ (161 mg, 1.31 mmol) and $NiCl_2$ (1 mg, 0.0077 mmol) in DMF (3 mL) was stirred at room temperature under Ar for 10 min, and to this was added a solution of **82** (156 mg, 0.262 mmol) in DMF (2 mL). The resulting mixture was stirred at room temperature for 40 h. After addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with EtOAc (3 × 20 mL), and the extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) to give **83** (97 mg, 79%) as a colorless oil: $[\alpha]^{27}_D$ +27.5° (c 1.4, $CHCl_3$); IR (neat) 3354, 2873, 2797, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3 H, d, J = 6.5 Hz, 18-Me), 1.20 (3 H, d, J = 5.9 Hz, 17-Me), 1.26 (3 H, s, 9-Me), 1.40 (3 H, s, acetonide Me), 1.41 (3 H, s, acetonide Me), 1.60 (3 H, s, 19-Me), 1.70–1.95 (4 H, m, 1-H_2, 2-H_2), 1.98–2.10 (3 H, m, part of 3-H_2, 12-H_2), 2.18 (1 H, br s, OH), 2.48–2.62 (2 H, m, 8a-H, 11-H), 2.78 (1 H, br d, J = 12.4 Hz, 5-H_{ax}), 3.15 (1 H, br t, J = 8.5 Hz, part of 3-H_2), 3.71 (1 H, br d, J = 12.4 Hz, 5-H_{eq}), 3.83 (1 H, d, J = 8.6 Hz, 15-H), 3.90 (1 H, dq, J = 8.6, 5.9 Hz, 16-H), 4.05 (1 H, s, 7-H), 4.53 and 4.56 (2 H, AB q, J = 12.4 Hz, CH_2Ph), 5.29 (1 H, br d, J = 9.6 Hz, 10-H), 5.41 (1 H, br t, J = 7.2 Hz, 13-H), 7.18–7.33 (5 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 16.9, 18.6, 20.8, 20.9, 22.8, 26.9, 27.5, 32.4, 35.8, 48.5, 54.3, 64.5, 66.3, 73.9, 75.9, 76.6, 89.2, 107.9, 127.0, 127.3 (2 carbons), 128.1 (2 carbons), 129.9, 131.4, 134.3, 135.4, 140.3; CIMS (isobutane) m/z 470 (MH^+), 454, 378; EIMS m/z (relative intensity) 454 (M^+ – Me, 4), 378 (M^+ – Bn, 100), 346 (8), 320 (3), 166 (10), 125 (16); HRMS calcd for $C_{28}H_{40}NO_4$ (M^+ – Me) 454.2957, found 454.2979.

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-6(*Z*)-[6(*R*),7(*R*)-dihydroxy-2(*R*),5-dimethyl-4(*E*)-octenylidene]-8-methyloctahydroindolizine (84). To a solution of **83** (85 mg, 0.18 mmol) in THF (1 mL) was added 3 N HCl (1 mL), and the resulting mixture was stirred at room temperature. After 20 min, the mixture was basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) to give **84** (71 mg, 91%) as a colorless oil: $[\alpha]^{28}_D$ +28.8° (c 1.9, $CHCl_3$); IR (neat) 3392, 2873, 2801, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3 H, d, J = 6.5 Hz, 18-Me), 1.11 (3 H, d, J = 6.3 Hz, 17-Me), 1.28 (3 H, s, 9-Me), 1.56 (3 H, s, 19-Me), 1.65–1.92 (4 H, m, 1-H_2, 2-H_2), 1.94–2.10 (2 H, m, 12-H_2), 2.34 (1 H, m, part of 3-H_2), 2.57 (1 H, m, 11-H), 2.65 (1 H, m, 8a-H), 2.85 (1 H, d, J = 12.3 Hz, 5-H_{ax}), 3.00 (1 H, m, part of 3-H_2), 3.51 (1 H, d, J = 12.3 Hz, 5-H_{eq}), 3.66 (1 H, d, J = 6.8 Hz, 15-H), 3.75 (1 H, m, 16-H), 4.07 (1 H, s, 7-H), 4.54 (2 H, s, CH_2Ph), 5.22 (1 H, d, J = 10.0 Hz, 10-H), 5.37 (1 H, br dd, J = 9.3, 6.0 Hz, 13-H), 7.20–7.33 (5 H, m, Ph); ^{13}C NMR (100 Hz, $CDCl_3$) δ 12.4, 18.6, 19.2, 21.1, 21.3, 22.9, 32.6, 35.6, 48.8, 54.5, 64.5, 66.4, 68.5, 75.4, 76.9, 82.3, 127.1, 127.2 (2 carbons), 127.5, 128.1 (2 carbons), 134.0, 134.1, 135.2, 140.1; CIMS (isobutane) m/z 430 (MH^+), 413, 384, 338; EIMS m/z (relative intensity) 429 (M^+, 1), 411 (0.4), 384 (M^+ – EtO, 0.7), 338 (M^+ – Bn, 100), 306 (12), 266 (23), 222 (17), 192 (6), 166 (18), 138 (12), 110 (20); HRMS calcd for $C_{24}H_{34}NO_3$ (M^+ – C_2H_5O) 384.2539, found 384.2551.

(+)-Allopumiliotoxin 339A (2). A solution of **84** (55 mg, 0.13 mmol) in THF (2 mL) was added to liquid NH_3 (5 mL) at –78 °C via a microsyringe. To this mixture was added Li (9 mg, 1.3 mmol) in small portions with stirring at –78 °C, and then the cooling bath was removed. After being stirred for another 15 min, the resulting purple-blue mixture was quenched by addition of NH_4Cl, and the ammonia was allowed to evaporate at room temperature. To the residue was added saturated aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–concentrated NH_4OH, 200:9:1) to give **2** (34 mg, 78%) as a colorless solid: mp 53–56 °C; $[\alpha]^{28}_D$ +38.8° (c 0.5, MeOH) (lit.[2b] $[\alpha]^{25}_D$ +29.4° (c 1.0, MeOH)), $[\alpha]^{28}_D$ +72.4° (c 0.66, $CHCl_3$) (lit.[5] $[\alpha]^{23}_D$ +68.2° (c 0.5, $CHCl_3$)); IR (neat) 3402, 2877, 2801, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3 H, d, J = 6.5 Hz, 18-Me), 1.12 (3 H, d, J = 6.3 Hz, 17-Me), 1.19 (3 H, s, 9-Me), 1.55 (3 H, s, 19-Me), 1.65–1.75 (4 H, m, 1-H_2, 2-H_2), 1.96–2.09 (2 H, m, 12-H_2), 2.26 (1 H, m, part of 3-H_2), 2.45–2.58 (2 H, m, 8a-H, 11-H), 2.68 (1 H, dd, J = 12.1, 1.1 Hz, 5-H_{ax}), 3.02 (1 H, dd, J = 6.3, 2.3 Hz, part of 3-H_2), 3.56 (1 H, d, J = 12.1 Hz, 5-H_{eq}), 3.66 (1 H, s, 7-H), 3.70 (1 H, d, J = 6.2 Hz, 15-H), 3.77 (1 H, quint, J = 6.3 Hz, 16-H), 5.24 (1 H, dd, J = 10.1, 1.1 Hz, 10-H), 5.32 (1 H, br t, J = 7.7 Hz, 13-H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 12.4, 19.3, 20.6, 21.19, 21.23, 22.7, 32.7, 35.4, 49.3, 54.3, 65.2, 68.3, 70.4, 80.8, 82.1, 127.2, 133.9, 135.1, 137.0; CIMS (isobutane) m/z 340 (MH^+), 322, 294; EIMS m/z (relative intensity) 339 (M^+, 2), 322 (3), 294 (5), 276 (6), 250 (2), 222 (14), 210 (8), 182 (27), 166 (3), 151 (12), 114 (18), 86 (34), 70 (100); HRMS calcd for $C_{19}H_{33}NO_4$ (M^+) 339.2410, found 339.2434.