Total Synthesis of Galantin I. Acid-Catalyzed Cyclization of Galantinic Acid

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Abstract: The proposed structure of galantin I, a peptide antibiotic isolated from *Bacillus pulvifaciens* as a mixture of congeners (**1a** with the D-ornithine residue and **1b** with D-lysine; **1a**/**1b** = 9/1), was shown to be incorrect by total synthesis. The substructure **3a**, named galantinic acid, was an artifact, and its correct structure was assumed to be the hydroxylated form, **20a** or **20b**, by spectroscopic comparisons of synthetic **1a** with natural galantin I. The synthesis of both diastereomers, **4a** and **4b**, again suggested that the sequence of the spermidine moiety of galantin I should be N^5,N^8. Finally, the correct structure of galantin I as **5a** was confirmed by the synthesis of diastereomers **5a** and **5b**. The synthesis of **5a** was accomplished in a convergent manner by the coupling of the protected forms of the constituent amino acids: D-ornithine, **6b**, D-alanine, **23b**, **11b**, **8c**, and **19a**. Galantinic acid residue **20a**, present in natural galantin I, was found to undergo cyclization with retention of its C3 configuration under the chemical degradation conditions to give the artifact **3a**. In order to elucidate the mode of cyclization of **20a** to **3a**, the synthesis of **20a** and its analogues was accomplished in a stereoselective manner from D-serine. The synthesis was characterized by the stereoselective epoxidation of hydroxymethyl (*Z*)-allylamine **34** and α,β-unsaturated δ-lactone **39**. Acidolysis of **20a**, **20b**, and their analogues suggested that the stereoselective cyclization of galantinic acid was initiated by the formation of δ-lactone **54**, which through the sequence of reactions should afford the artifact **3a**.

Introduction

Galantin I, a peptide antibiotic isolated from a culture broth of *Bacillus pulvifaciens* as a mixture of congeners with the D-ornithine (Orn) and D-lysine (Lys) residues (Orn/Lys = 9/1), attracted significant interest from chemists in view of its potent antibacterial activity and its unique polyamine structure.[1] The original structure of galantin I was assigned as a mixture of **1a** and **1b** by the combination of chemical degradation studies[2] and the syntheses of its constituent unusual amino acids, galantinamic acid (Glm) (**2**)[3] and galantinic acid (Gla) (**3a**).[4,5] However, our continuous efforts aimed at the total synthesis of galantin I showed that the proposed structure, **1a** and **1b**, was incorrect and that the structure of **3a**, derived from the chemical degradation studies of galantin I, was that of an artifact. Moreover, the sequence of the spermidine residue coupled with glycine was not N^4,N^8 [Spe(3,4)] but was N^5,N^8 [Spe(4,3)] as shown in Figure 1. Described herein is the correct structure of galantin I, a mixture of **5a** and **5c**, which was confirmed by the convergent synthesis of the possible structures, speculated from the spectroscopic studies of natural galantin I.[6] The fact that Gla (**20a**) dehydrated stereoselectively to the cyclized adduct **3a** under the degradation conditions initiated the studies regarding its stereoselective synthesis and its acid-catalyzed cyclization.

Results and Discussion

1. Reinvestigation of the Structure of Galantin I. The synthesis of the proposed structure **1a** was performed by the initial preparation of enantiomerically pure constituent amino acids and subsequent coupling of these moieties (vide infra).

In order to spectroscopically compare the synthetic **1a** with natural galantin I (Orn), we first examined the separation of authentic natural galantin I (Orn) from its D-lysine congener using HPLC.[7] The crude sample of galantin I, donated by Shiba, was fractionated on a semipreparative scale to give pure galantin I both with D-ornithine (retention time, 61 min) and with D-lysine.[7] The synthetic product with structure **1a** was different from natural galantin I (Orn) by comparison of their ^{1}H NMR and MS data. Both the 500-MHz ^{1}H NMR data and HPLC retention time (that of synthetic **1a**, 71 min)[7] were different from that of natural galantin I. These results led us to reinvestigate the structure of natural galantin I, synthetically as well as spectroscopically.

The MS (SIMS) data of each congener of natural galantin I showed the parent ion peak at 981 [$(M + H)^+$] for galantin I (Orn) and 995 [$(M + H)^+$] for galantin I (Lys), respectively, which correspond to the proposed molecular formula plus H_2O. Furthermore, comparison of the ^{1}H NMR spectrum of natural galantin I with that of synthetic **1a** revealed that the signals corresponding Gla were much different from each other (Figure 2). For example, the signals of the two hydrogens on C4 of the Gla of natural galantin I appeared at almost the same chemical shift (δ 1.6, m), while those for **1a** appeared at δ 1.6 and 2.3 (each 1 H). These data suggested that the correct structure of Gla was not the cyclic form **3a** but an acyclic form, either 3*S*-**20a** or 3*R*-**20b**. This cyclized under the degradation conditions to give **3a**. Therefore, it was concluded that isolated **3a** was an artifact. Since only a single diastereomer **3a** was isolated, Gla's cyclization appeared to be a stereospecific process with either retention or inversion of the C3 configuration.

From the spectroscopic studies, it was not possible to determine whether natural galantin I contained 3*S*-**20a** or 3*R*-**20b** as the Gla residue. Furthermore, an authentic sample of Gla was not available because of its cyclization to afford **3a** under the chemical degradation conditions. Therefore, the synthesis of both diastereomer **4a** having 3*S*-**20a** and diastereomer **4b** having 3*R*-**20b** was required. In addition to the uncertainty concerning the Gla moiety, the reason why the ^{1}H NMR chemical shifts and coupling patterns of the spermidine residue of **1a** were different from those of natural galantin I (Figure 2) was not obvious.[8] The spectral data of

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(2) (a) Ando, T.; Terashima, S.; Kawata, M.; Teshima, T.; Wakamiya, T.; Shiba, T. *Peptide Chemistry 1980*; Okawa, K., Ed.; Protein Research Foundation: Osaka, 1981; p 113. (b) Wakamiya, T.; Ando, T.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 142. (c) Wakamiya, T.; Terashima, S.; Kawata, M.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1422.

(3) Hori, K.; Ohfune, Y. *J. Org. Chem.* **1988**, *53*, 3886.

(4) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.

(5) (a) Golebiowski, A.; Kozak, J.; Jurczak, J. *Tetrahedron Lett.* **1989**, *30*, 7103. (b) Kano, S.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1990**, *31*, 13. (c) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240. (d) Ikota, N. *Heterocycles* **1991**, *32*, 521.

(6) Parts of this work were published in preliminary reports: (a) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 3183. (b) Sakai, N.; Ohfune, Y. *Peptide Chemistry 1989*; Yanaihara, N., Ed.; Protein Research Foundation: Osaka, 1990; p 227. (c) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *32*, 4151.

(7) Column: UNISIL PACK $5C_{18}$ (G. L. Sciences Inc., Tokyo, Japan); column dimensions, 10.7 cm i.d. × 25 cm; flow rate, 1 mL/min; eluent, 1% CH_3CN/0.1% TFA in H_2O. Retention time of each compound: **1a**, 71 min; **4a**, 54 min; **4b**, 57 min; natural galantin I (Orn) **5a**, 61 min; **5b**, 65 min; natural galantin I (Lys) **5c**, 75 min.

(8) The sequence of the Spe(3,4) residue in the original structure was elucidated by the microbial method.[2a]

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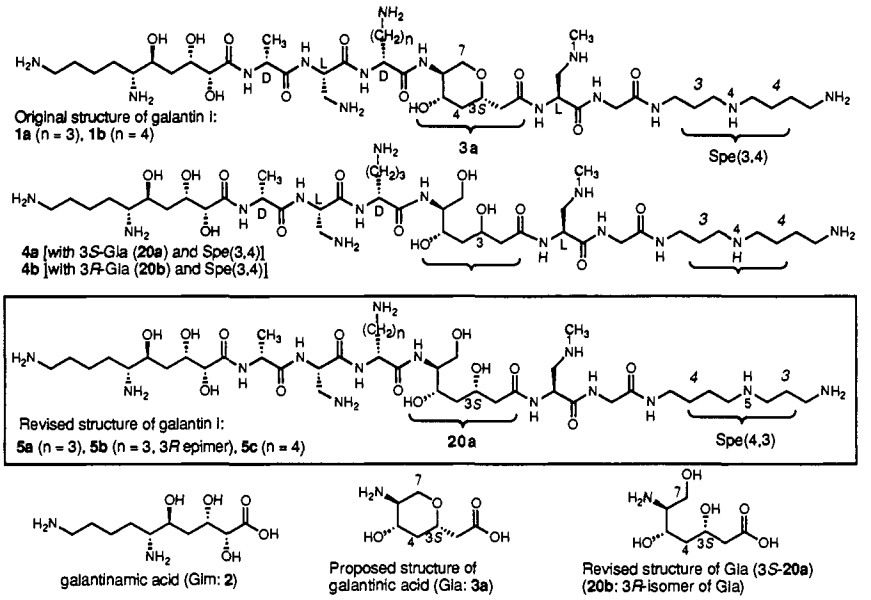


Figure 1.

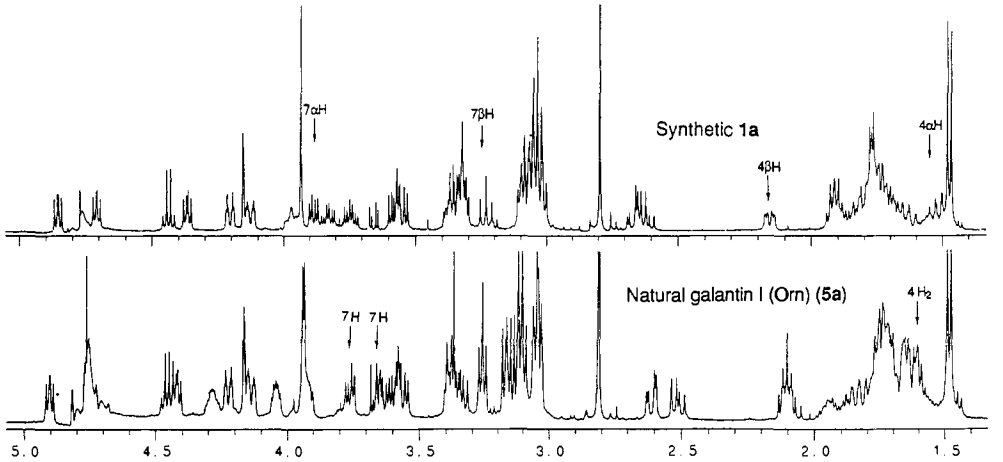


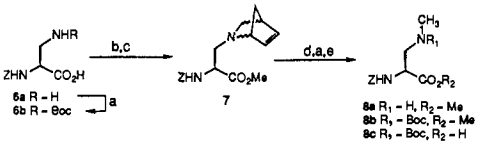
Figure 2. ^{1}H NMR (500 MHz, D_2O) spectra of synthetic **1a** and natural galantin I (Orn) (**5a**).

synthetic **4a** and **4b** suggested that the correct sequence of spermidine should be N^5,N^8 and not N^4,N^8 (see the supplementary material). Finally, the correct structure of galantin I (Orn) was established to be **5a** by the synthesis of both diastereomers, **5a** and **5b**.

2. Synthesis of the Constituent Amino Acids and Spermidine Residue of Galantin I. The syntheses of the requisite constituent amino acids, N^{β}-methyl-L-α,β-diaminopropionic acid (N^{β}-Me-L-A_2Pr),[9] protected forms of both epimers of Gla, **19a** and **19b**, and the spermidine residue [Spe(4,3)], are described. To accomplish the synthesis of **5a** and **5b** in a liquid phase, all synthetic fragments were appropriately protected: the N-terminal of all amino acids was protected by the benzyloxycarbonyl (Z) group, and the other amino groups were protected by the *tert*-butoxycarbonyl (Boc) group.

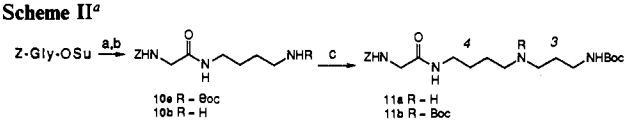
Synthesis of Protected N^{β}-Me-L-A_2Pr (8c). The synthesis of **8c** started from N^{α}-(benzyloxycarbonyl)-L-α,β-diaminopropionic acid (Z-L-A_2Pr; **6a**).[10] The key transformation was the use of an efficient N-monomethylation procedure reported by Grieco et al.[11] Thus, the methyl ester of **6a**, prepared by the esterification of **6b** with diazomethane followed by removal of the Boc group with TFA, was treated with aqueous formaldehyde and cyclopentadiene to give a mixture of cycloadducts **7** (endo/exo = 1/1) (Scheme I). A reductive retro-Diels–Alder reaction of **7** with

Scheme I[a]



[a] (a) Boc_2O, Et_3N, dioxane/H_2O (1/1), room temperature, 14 h. (b) Diazomethane, Et_2O, room temperature (100% from **6a**). (c) (1) TFA, CH_2Cl_2, room temperature, 20 min; (2) 35% aqueous formaldehyde, cyclopentadiene, room temperature, 1 h. (d) TFA, triethylsilane, $CHCl_3$, room temperature, 14 h (59% from **6b**). (e) 0.5 N NaOH, THF, 6 h, 0 °C (100%).

Scheme II[a]



[a] (a) 2 equiv of putrescine, DMF, 80 °C, 10 min, and then Boc_2O, Et_3N, room temperature, 4 h (50%). (b) (1) TFA, CH_2Cl_2, room temperature, 20 min; (2) *N*-Boc-3-amino-1-propanal, $NaBH_3CN$, MeOH, pH 8, room temperature, 13 h; (3) Boc_2O, Et_3N, dioxane/H_2O (1/1), room temperature, 3 h (63% from **10a**).

triethylsilane/TFA gave the desired N-monomethylated product **8a** which, upon protection with the Boc group [*tert*-butyl dicarbonate (Boc_2O)/triethylamine (Et_3N)], gave mono-N-methylated **8b** (59% yield from **6a**). Hydrolysis of the resulting

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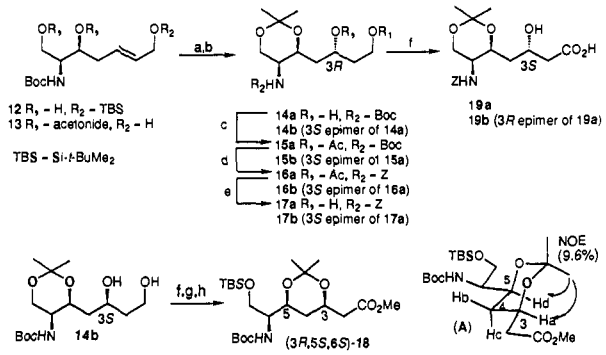
Scheme III[a]



[a] (a) (1) 2,2-Dimethoxypropane, acetone, CSA, room temperature, 3 h; (2) *n*-Bu_4NF, THF, room temperature, 3 h; (3) MCPBA, CH_2Cl_2, 0 °C, 1.5 h (76% from **12**). (b) $LiAlH_4$, Et_2O, 0 °C, 1 h (**14a**, 13%; **14b**, 24%). (c) Acetic anhydride, pyridine, room temperature, 14 h. (d) (1) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 10 min; (2) benzyl bromide, *n*-Bu_4NF, THF, 0 °C, 1 h (**16a**, 75% from **14a**; **16b**, 73% from **14b**). (e) 0.1 equiv of K_2CO_3, MeOH, room temperature, 2 h. (f) PtO_2, O_2, dioxane/H_2O (2/1), 45 °C, 4 h (**19a**, 83% from **16a**; **19b**, 96% from **16b**). (g) Diazomethane, Et_2O (50% from **14b**). (h) (1) CSA, MeOH, room temperature, 14 h; (2) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 10 min; (3) CSA, 2,2-dimethoxypropane, benzene, room temperature, 10 min (26%, 3 steps).

methyl ester yielded, quantitatively, the desired **8c**.

Synthesis of Protected Glycyl Spermidine [Spe(4,3)] (11b). The synthesis of **11b** started with the condensation of *N*-(benzyloxycarbonyl)glycine succinimido ester (Z-Gly-OSu) and putrescine (Scheme II). Treatment of Z-Gly-OSu with 2 equiv of putrescine/*N*,*N*-dimethylformamide (DMF), 80 °C, 10 min, gave a mixture of mono- and diglycyl putrescine and putrescine. In order to isolate the desired monoglycyl putrescine **10b**, the mixture was converted to the corresponding *N*-Boc derivatives. The resulting mixture was readily separated by silica gel column chromatography to give **10a** in 50% overall yield. This compound, upon treatment with TFA, gave *N*-Z-glycyl putrescine **10b**. Reductive coupling of **10b** with *N*-Boc-3-aminopropanal was effected by $NaBH_3CN$/MeOH[12] to give Z-Gly-Spe(4,3) **11a**. Finally, the imino group of **11a** was protected with the Boc group (Boc_2O/Et_3N) to give the di-Boc compound **11b** (69% in 3 steps).[13]

Synthesis of 3*S*-19a and 3*R*-19b. In order to determine whether the structure of Gla had the 3*S* or 3*R* configuration, the synthesis of galantin I, containing diastereomers both with 3*S*-**20a** and with 3*R*-**20b**, was crucial. Therefore, the synthesis of both 3*S*-**19a** and 3*R*-**19b** was performed with the protected forms of **20a** and **20b**, respectively. The syntheses of both **19a** and **19b** started with **12**, a precursor of our previous synthesis of **3a**.[4] The amino alcohol **12** was initially transformed to the allyl alcohol **13** in two steps: (1) protection of the hydroxyl group as an acetonide by treatment with *dl*-camphorsulfonic acid (CSA)/2,2-dimethoxypropane and (2) removal of the *tert*-butyldimethylsilyl (TBS) group with *n*-Bu_4NF/tetrahydrofuran (THF). Epoxidation of **13** with 3-chloroperoxybenzoic acid (MCPBA) produced, as expected, a 1/1 mixture of epoxides which, without separation, was reduced with $LiAlH_4$/diethyl ether (Et_2O) to give a mixture of alcohols, **14a** (13% yield, R_f = 0.44, MeOH/$CHCl_3$ = 9/1) and **14b** (24%, R_f = 0.50). The structures of these alcohols were confirmed by converting the less polar isomer **14b** to the acetonide **18**. The ^1H NMR data and the extensive NOE experiments of **18** revealed that the C3 configuration of **18** was *R*, as evidenced by its large *J* values ($J_{H_a\text{-}H_b}$ = $J_{H_b\text{-}H_d}$ = 13 Hz) and NOEs between the methyl group of the acetonide and H_a and H_d (each ca. 9.6%) (Scheme III, structure A). Thus, the structure of **14b** was unambiguously established to be the 3*S* isomer. Accordingly, the more polar isomer **14a** was shown to have 3*R* stereochemistry as depicted.

Examined next was the conversion of the Boc groups of **14a** and **14b** to the corresponding Z groups. This transformation was characterized by an initial conversion of the Boc group to the *tert*-butyldimethylsilyl carbamate and subsequent electrophilic substitution of this reactive species with benzyl bromide in the presence of fluoride ion ($NHCO_2$-*t*-Bu → $NHCO_2SiMe_2$-*t*-Bu → $NHCO_2CH_2Ph$).[14] Thus, after protection of the diol moiety of **14a** with acetic anhydride/pyridine, the resulting diacetate **15a** was allowed to react with (1) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/2,6-lutidine and (2) benzyl bromide/*n*-Bu_4NF to give the desired *N*-Z compound **16a** (75% yield, 3 steps). This was treated with K_2CO_3/MeOH to give diol **17a** (100%). Finally, PtO_2/O_2 oxidation[15] of **17a** yielded the desired (3*S*)-3-hydroxyheptanoic acid derivative **19a** (83%). The conversion of 3*S*-**14b** to 3*R*-**19b** was performed in the same manner as described above (56% overall yield).

3. Synthesis of Galantin I (Orn) (5a) and Galantin I (Lys) (5c). To determine both the configuration at C3 of Gla and the sequence of the spermidine residue (vide supra), we next examined the synthesis of the diastereomers **5a** and **5b**, which was carried out in a convergent manner. The protected forms of both **5a** and **5b** were constructed by coupling of the C-terminal acid of the left-half fragment with the N-terminal amine of the right-half fragment, respectively. The former was composed of a protected form of galantinamyl-D-alanyl-L-α,β-diaminopropionyl-D-ornithine (Glm-D-Ala-L-A_2Pr-D-Orn-OH, **24b**) and the latter, (3*S*)-galantinyl-N^β-methyl-L-α,β-diaminopropionylglycylspermidine [(3*S*)-H-Gla-N^β-Me-L-A_2Pr-Gly-Spe(4,3), **27a**] or its 3*R* epimer **27b** (Scheme IV).

Synthesis of the Left Half, 24b. The coupling of N^ϵ-(*tert*-butoxycarbonyl)-D-ornithine methyl ester (H-N^ϵ-Boc-D-Orn-OMe) with N^α-Z-N^β-Boc-L-A_2Pr-OH (**6b**) using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC·HCl)[16] gave dipeptide **21** which, upon treatment with H_2/Pd–C, gave the N-terminal free dipeptide of **21**. Condensation of this with *N*-Z-D-Ala-OH in the same manner as above gave tripeptide **22**.

On the other hand, protected Glm **23b** was prepared from the previously reported **23a**[3] in two steps: (1) CSA/2,2-dimethoxypropane and (2) 1 N NaOH/THF (90% yield).

After removal of the Z group of **22** (H_2/Pd–C), it was condensed with **23b** by treatment with diphenylphosphoryl azide[17] (DPPA)/Et_3N/DMF to furnish, in 68% yield, the desired left-half peptide **24a**.

Synthesis of the Right Half, 3*S*-27a and 3*R*-27b. After removal of the Z group of Z-Gly-di-Boc-Spe(4,3) **11b**, the resulting amine was condensed with protected N^β-Me-L-A_2Pr-OH (**8c**) using diethyl phosphorocyanidate[18] (DEPC) to give, in 62% yield, the desired tripeptide **25**. Removal of the Z group of **25** (H_2/Pd–C) followed by coupling with 3*S*-Gla-OH **19a** using DPPA/Et_3N gave the right-half peptide 3*S*-**26a** (55% yield). Also, the synthesis of its 3*R* isomer **26b** was performed by the use of 3*R*-**19b** in the same manner as above.

Synthesis of Galantin I (Orn) (5a) and Its Lys Congener (5c). Hydrolysis of **24a** (1 N NaOH) gave the C-terminal acid **24b**, the left-half peptide. This was coupled with amine **27a** (prepared from **26a** using H_2/Pd-C) in the presence of DPPA/Et_3N to give a protected form of the desired 3*S*-**28a**. However, the yield was quite low (~10%) probably due to a prolonged reaction time (several days) and relatively high concentrations of Et_3N, which induced side reactions such as the decomposition of an intermediary active ester (mainly Curtius type rearrangement).[19] This was overcome by the use of powdered $NaHCO_3$ instead of Et_3N as the base.[20] The reaction proceeded smoothly (0 °C, 22 h) to

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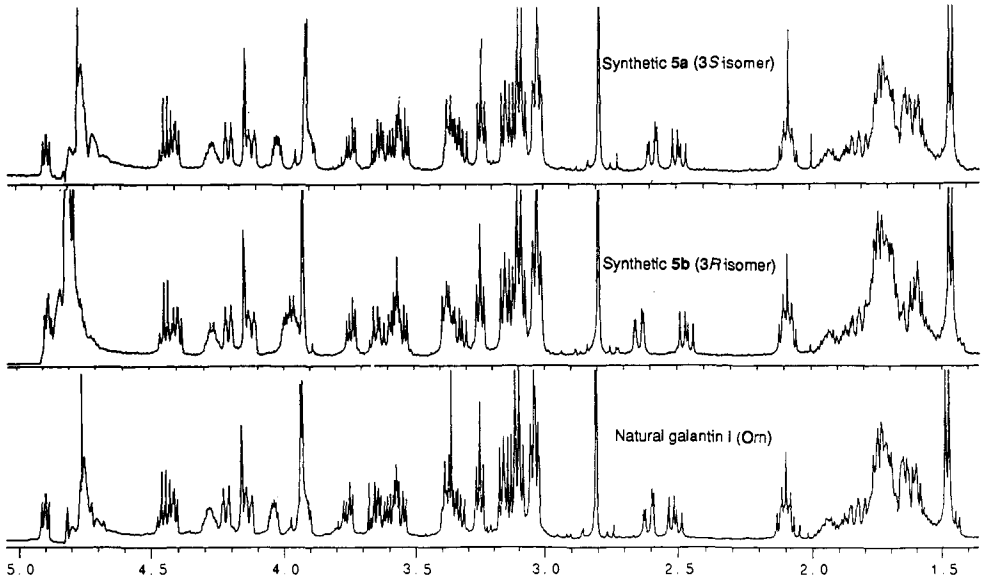
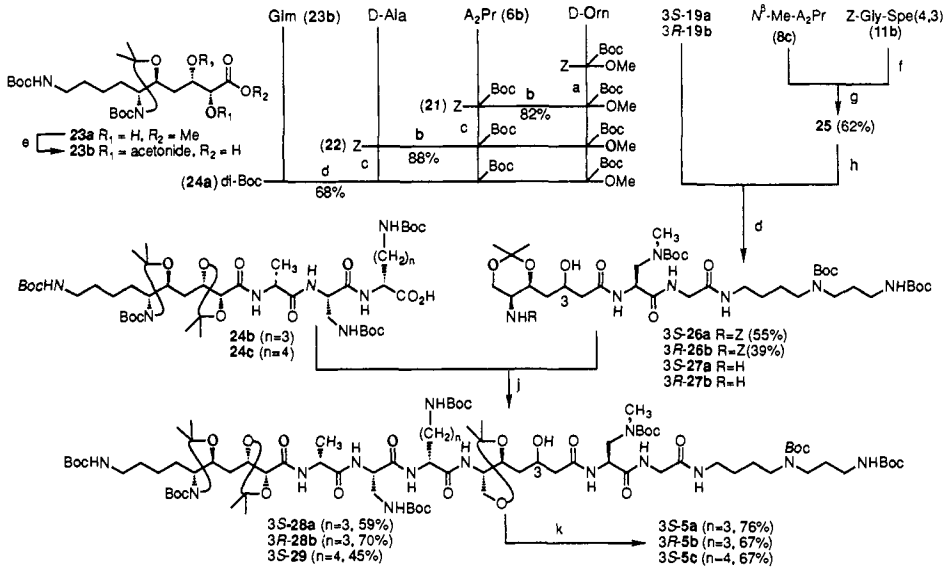


Figure 3. ^1H NMR (500 MHz, D_2O) spectra of synthetic **5a**, its 3*R* epimer **5b**, and natural galantin I (Orn) (**5a**).

Scheme IV[a]



[a] (a) H_2/10% Pd–C, MeOH, room temperature, 14 h. (b) 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC·HCl), CH_2Cl_2, room temperature, 2 h. (c) a, 17 h (99%). (d) Diphenylphosphoryl azide (DPPA), Et_3N, DMF, 0 °C, 24 h. (e) (1) CSA, 2,2-dimethoxypropane, acetone, room temperature, 20 h (90%); (2) 1 N NaOH, THF, 0 °C, 14 h (**23b** was used without further purification for the peptide coupling). (f) a, 91%. (g) Diethyl phosphorocyanidate (DEPC), Et_3N, DMF, 0 °C, 16 h. (h) a, 99%. (i) a, 71%. (j) DPPA, $NaHCO_3$ powder, DMF, 0 °C, 22 h. (k) TFA, CH_2Cl_2, room temperature, 3 h.

give, in 59% yield, the desired **28a**. Because the reaction medium was heterogeneous ($NaHCO_3$ is slightly soluble in DMF), a low concentration of the base would prevent such side reactions. Finally, all of the protecting groups of **28a** were removed with TFA simultaneously to give 3*S*-**5a**. The same sequence of coupling reactions as above, starting from 3*R*-**26b**, allowed the synthesis of 3*R*-**5b**.

Both diastereomers **5a** and **5b** were diastereomerically pure and were clearly distinguishable by HPLC analysis[7] and by their ^1H NMR spectra. Comparisons of their ^1H NMR data and HPLC retention times with those of the natural galantin I (Orn) clearly indicated that the structure of **5a** was the natural form which possesses 3*S*-**20a** and Spe(4,3) (Figure 3). Thus, the structure of galantin I (Orn) was confirmed by its total synthesis.

The above synthesis suggested that the structure of the lysine congener of galantin I was **5c**, which possesses 3*S*-**20a** (Gla) and Spe(4,3). This was confirmed by the synthesis of **5c**, which was carried out by the coupling of amine 3*S*-**26a** with the left-half peptide acid **24c** having the D-lysine residue instead of D-ornithine. The coupling proceeded smoothly in the same manner as that of the ornithine residue to give **29** (45%) which, upon deprotection with TFA, gave **5c**. Both the MS data and HPLC retention time[7] of synthetic **5c** were completely identical with those of natural galantin I (Lys). Thus, the correct structure of galantin I (Lys) was shown to be **5c**.[21]

4. Synthesis and Acid-Catalyzed Cyclization of (−)-Galantinic Acid (20a). The structure of Gla was revised as 3*S*-**20a**. This indicated that, under the peptide bond breaking conditions, an artifact **3a** was produced from **20a** with retention of its C3 configuration. In order to accomplish a stereoselective route to the

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(21) Since only minute quantities of galantin I (Lys) were isolated, the ^1H NMR spectrum, which could be superimposable with the synthetic one, was not obtained. However, its MS (SIMS) data and HPLC retention time supported the theory that the structure of natural galantin I (Lys) should be that of **5c** as depicted in Figure 1 (also see the supplementary material).

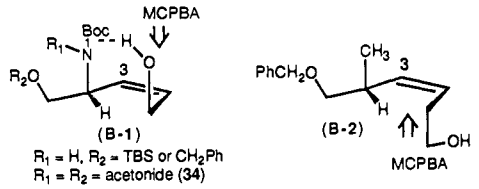
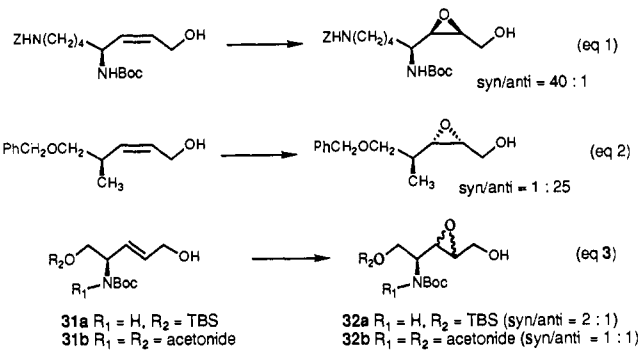


Figure 4.

synthesis of Gla and to elucidate the mechanism of acid-catalyzed cyclization of **20a** to **3a**, our next goal was the synthesis of Gla and its analogues.

Synthesis of Galantinic Acid (20a). The previous synthesis of Gla and its C3 epimer, **19a** and **19b**, respectively, was in a masked form and was nonstereoselective. We planned to synthesize Gla via the α,β-unsaturated δ-lactone **39** starting from the readily available L-serinal derivative **30**.

In the previous synthesis of galantinamic acid (**2**), epoxidation of the hydroxymethyl (*Z*)-allylamine with MCPBA stereoselectively yielded the *syn*-epoxide (syn/anti = 40/1, eq 1).[3,22] Contrary to eq 1, the compound, which has a methyl group instead of an amino group, was shown to exhibit anti selectivity (syn/anti = 1/25, eq 2).[23] The mechanism of the latter case was well-



documented as the less hindered attack (*re* face on C3) of an internal chelate complex of MCPBA on the C–C double bond (Figure 4, B-2). On the other hand, the example shown in eq 1 indicated that an MCPBA complex attacked from the more hindered *si* face on C3. The protection of the hydroxyl group in eq 1 with the TBS group resulted in a decrease in both yield (>20%, 3 days) and product ratio (~3/1). Therefore, the high syn selectivity in the epoxidation of hydroxymethyl (*Z*)-allylamines was attributed to the fact that the epoxidation proceeded through a chelation complex B-1 to result in the predominant formation of the *syn*-epoxide. The (*E*)-allyl alcohols, **31a** and **31b**, provided a 1–2/1 mixture of syn and anti epoxides, **32a** and **32b**, respectively (eq 3). Thus, the epoxidation of hydroxymethyl (*Z*)-allylamine appeared to be a potential method for the preparation of the 1,2-syn amino hydroxy system which is present in Gla (**20a**) and in many naturally occurring compounds.

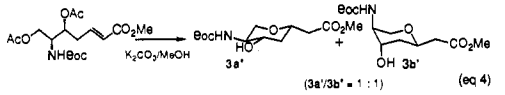
The requisite 1,2-syn amino hydroxy system of Gla was constructed using the abovementioned method. Initially, the L-serinal derivative **30**[24] was converted to the hydroxymethyl (*Z*)-allylamine **34** in 2 steps (60%). The epoxidation of **34**, in spite of the lack of its amide hydrogen, was syn-selective to give, as a sole product, the desired epoxide **35** in 94% yield. The structure of **35**, having a 3*R* configuration, was confirmed by converting it to the known acetonide **36**.[25] The exclusive formation of the *syn*-epoxide **35** supported our initial assumption that the epoxidation proceeded through the transition-state structure (B-1).

Next, elongation of the two-carbon unit on the alcohol **35** was performed in two steps: (i) Swern oxidation[26] ($(COCl)_2$/dimethyl sulfoxide (DMSO), −90 °C) and (ii) Wittig olefination (Ph_3PCHCO_2Me/benzene). The product was composed of a mixture of *E* and *Z* unsaturated esters **37** (*E*/*Z* = 2/1). The mixture was allowed to react with $Na[PhSeB(OEt)_3]$[27a] in ethanol to give, in 97% yield, the desired *E* β,γ-unsaturated ester **38**. The reaction also gave as a byproduct a small amount of the corresponding ethyl ester (~10%). The ester **38**, upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/benzene, gave a mixture of desired α,β-unsaturated δ-lactone **39** (46% yield), starting material **38**, and *E* α,β-unsaturated ester **40a** (**38**/**39**/**40a** = 1/4/4). Since the treatment of **40a** under the same reaction conditions provided the same product ratio, **39** could be produced via the *Z* α,β-unsaturated isomer **40b**. The *Z* isomer **40b** could not be detected in the reaction mixture, probably because this species cyclized immediately to the δ-lactone **39**. Recovered **38** and its isomerized **40a** were recycled to afford **39**.

Epoxidation of **39** with *t*-BuOOH in the presence of a catalytic amount of aqueous benzyltrimethylammonium hydroxide (Triton B) was highly stereoselective, giving epoxy lactone **41**. The yield was 42%, but 52% of the starting material **39** was recovered and recycled. Reductive cleavage of the epoxide **41** was effected with 3 equiv of PhSeH, prepared from 3 equiv of $Na[PhSeB(O\text{-}i\text{-}Pr)_3]$ and 3 equiv of AcOH,[27] to give 3-hydroxy δ-lactone **42a** as the sole product. The configuration at C3 of **42a** was *R*, as shown by converting the epoxide **41** to the acetonide **18** (vide supra). Thus, the structure of the epoxide **41** was unambiguously determined to be 2*R*,3*R*. The reductive opening of the epoxide **41** with $Na[PhSeB(OEt)_3]$ using ethanol as the solvent was accompanied by the opening of the lactone ring to yield its corresponding ethyl ester **43**. The use of 2-propanol prevented such a reaction, probably due to its bulky nature.[27b] Therefore, exclusive formation of the epoxide **41** can be attributed to an axial attack[28] of the reagent as depicted (Scheme V, structure C).

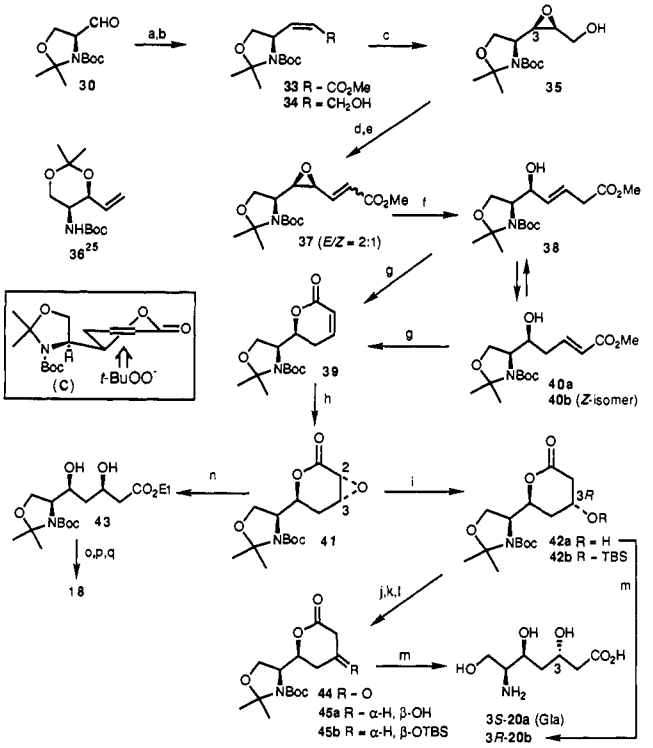
The structure of **42a** corresponded to the 3*R* isomer of Gla. Therefore, the conversion of **42a** to its 3*S* isomer **45a** by a sequential oxidation–reduction of the hydroxyl group at C3 was examined next. Initial attempts to oxidize **42a** were accompanied by difficulties such as low yields due to β-elimination of the hydroxyl group of **42a** or overoxidation of the product. However, oxidation of **42a** with trifluoroacetic anhydride (TFAA)/DMSO[29] gave ketone **44**, which was immediately reduced with $NH_3{\cdot}BH_3$[30] to give an inseparable mixture of **45a** and **42a** with moderate stereoselectivity (76% yield from **42a**; **45a**/**42a** = 3/1, ratio determined by ^1H NMR). However, the corresponding silyl ether **45b** and its C3 epimer **42b** (TBSOTf/2,6-lutidine, 0 °C) were separable by chromatography. Finally, exposure of **45b** to TFA followed by treatment with Dowex 50Wx4 (eluent, 1 N NH_3) gave, in quantitative yield, the desired **20a**. The C3 epimer of Gla **20b** was also obtained from **42a** by the same treatment as above. Thus, the synthesis of both Gla and its C3 epimer was accomplished starting from a chiral serinal derivative **30**.

Acid-Catalyzed Cyclization of Galantinic Acid and Its Analogues. In our previous synthesis of the cyclized adduct **3a**, Michael addition of the C7 alkoxy group to C3 was nonstereoselective, giving a 1/1 mixture of diastereomers **3a′** and **3b′** (eq 4).[4] This



(22) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311.
(23) Nagaoka, N.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(24) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(25) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133. Synthetic procedure of **36** from **35**: (1) $LiAlH_4$, Et_2O, 0 °C, 1 h, then room temperature, 2 h (78%); (2) *o*-nitrobenzeneselenenyl cyanide, tributylphosphine, pyridine, THF, room temperature, 1 h (70%); (3) 30% aqueous H_2O_2, CH_2Cl_2, room temperature, 12 h (100%); (4) *p*-toluenesulfonic acid, MeOH, room temperature, 2 h; (5) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C, 14 h (71%, 2 steps).
(26) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Tidwell, T. T. *Synthesis* **1990**, 857.
(27) (a) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293. Personal communication from Professor Masaaki Miyashita, Nagasaki University, whom we gratefully acknowledge. (b) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539.
(28) Deslongshamp, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 209–290.
(29) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Smith, A. B., III.; Levenberg, P. A. *Synthesis* **1981**, 567.
(30) Hausler, J. *Liebigs Ann. Chem.* **1983**, 982.

Scheme V[a]



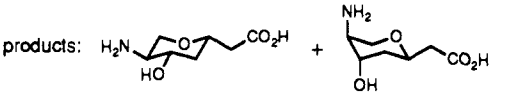
[a] (a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6, THF, −78 °C, 2 h (82%). (b) *i*-Bu_2AlH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, −78 °C, 1.5 h (73%). (c) MCPBA, CH_2Cl_2, 0 °C, 12 h (67%). (d) $(COCl)_2$, DMSO, CH_2Cl_2, −90 °C, 15 min, and then Et_3N, −90 °C, 10 min (87%). (e) Ph_3PCHCO_2Me, benzene, room temperature, 14 h (92%). (f) Na[$PhSeB(OEt)_3$], EtOH, room temperature, 1 h (94%). (g) 0.05 equiv of DBU, benzene, reflux, 60 h (**39**, 46%). (h) *t*-BuOOH, 0.1 equiv of 40% aqueous solution of benzyltrimethylammonium hydroxide (Triton B), THF, 0 °C, 15 min (**41**, 42% and **39**, 54%). (i) PhSeH, 2-PrOH, room temperature, 15 min (94%). (j) 1.5 equiv of TFAA, DMSO, CH_2Cl_2, −78 °C, 15 min, 3 equiv of Et_3N (dropwise addition over 30 min), −78 °C, 15 min. (k) $NH_3{\cdot}BH_3$, citric acid, THF/H_2O (10/1), room temperature, 1 h (76% from **42a**; **45a**/**42a** = 3/1). (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 15 min (64%). (m) (1) TFA, CH_2Cl_2, room temperature, 15 min; (2) Dowex 50Wx4 (elution with 1 N NH_3) (100%). (n) 3 equiv of Na[$PhSeB(OEt)_3$], 0.5 equiv of AcOH, EtOH, room temperature, 5 min (94%). (o) CSA, MeOH, room temperature, 48 h (52%). (p) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 10 min (46%). (q) CSA, 2,2-dimethoxypropane, benzene, room temperature, 5 min (73%).

result was in sharp contrast to that of the acidic degradation of natural galantin I, which produced the cycloadduct **3a** as the sole product *with retention of its C3 configuration.* With synthetic Gla and its analogues in hand, we next examined the acid-catalyzed cyclization of these compounds in order to elucidate the stereoselective cyclization of Gla (Scheme VI).

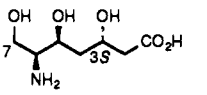
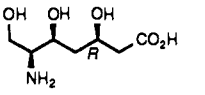
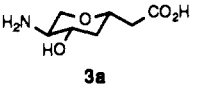
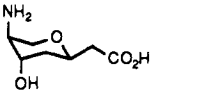
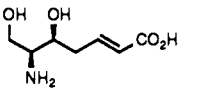
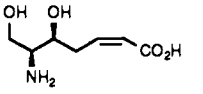
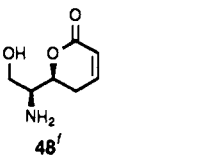
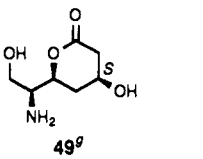
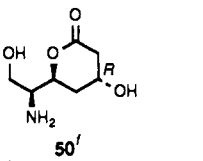
The following are hypothetical pathways that would afford **3a**: (a) substitution at C7 by the C3 hydroxyl group; (b) substitution at C3 by the C7 hydroxyl group in an S_N1 manner; (c) β-elimination of the C3 hydroxyl group followed by stereoselective 1,4-addition of the C7 hydroxyl group to the resulting α,β-unsaturated carboxylic acid derivative; and (d) stereospecific formation of the axial adduct **3b** in an S_N2 manner followed by conversion (e) to the thermodynamically more stable isomer **3a**. Also, the isomer **3b** would result from an S_N1 mechanism (b′) and a Michael addition (c′).

Thus, Gla **20a** and its analogues were treated under the degradation conditions of galantin I (6 N HCl, sealed tube, 110 °C, 10 h), as summarized in Table I. It was found that Gla itself provided a mixture of the cyclized products, equatorial isomer **3a**, and axial isomer **3b** (77%, **3a**/**3b** = 9/1). No starting material **20a** was detected in the reaction mixture. This selectivity was much greater than that of the base-catalyzed Michael addition

Table I. Acid-Catalyzed Cyclization of Gla (**20a**) and Its Analogues

products:  +

3a (equatorial adduct) **3b** (axial adduct)

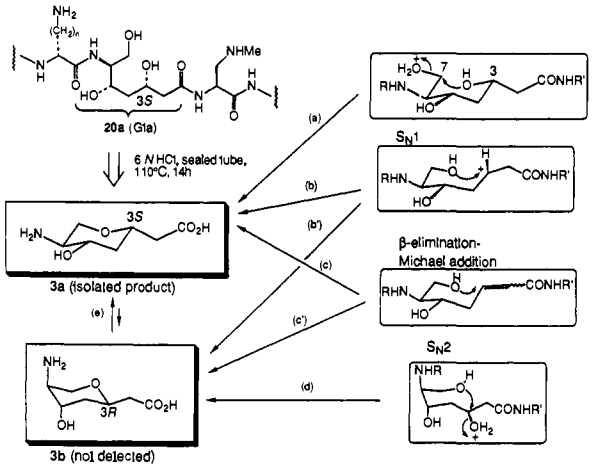
entry	starting material	product ratio[a] (**3a**:**3b**)	yield[b] (%)
1	**5a** (galantin I)	**3a** sole product	
2	 **20a** (galantinic acid)	9:1	77
3	 **20b**	11:1	42
4	 **3a**	8:1	100
5	 **3b**	2:7[c]	38
6	 **46**[d]	2:1	88
7	 **47**[e]	9:1	42
8	 **48**[f]	10:1	80
9	 **49**[g]	11:1	100
10	 **50**[f]	11:1	99

[a] The product ratios (**3a**/**3b**) were determined by 270-MHz ^1H NMR (D_2O) spectroscopy. [b] Isolated yields as a mixture of **3a** and **3b**. [c] The ratio was determined by converting the products to the corresponding compounds **3a**′ and **3b**′ (see eq 4). [d] Prepared from **40a** by hydrolysis (0.5 N NaOH) and used as its *N*-Boc acetonide. [e] Prepared from **39** by hydrolysis (0.5 N NaOH) and used as its *N*-Boc acetonide. [f] Used as its *N*-Boc acetonide. [g] Prepared from **45b** with TFA.

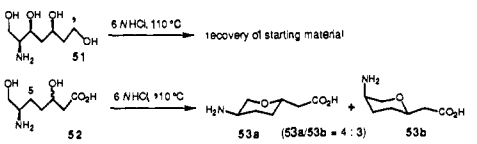
to the unsaturated ester (eq 4). The 3*R* isomer of Gla, **20b**, also gave a mixture of **3a** and **3b** (**3a**/**3b** = 11/1). Since not only Gla but also its 3*R* isomer **20b** predominantly produced **3a**, pathway a could be ruled out.

The conversion of **3b** to its thermodynamically more stable isomer **3a**, path e, under the reaction conditions was also ruled out by the following experiments (entries 4 and 5). Treatment of the equatorial isomer **3a** produced almost the same ratio of the product mixture (8/1) as from **20a**. On the other hand, the axial isomer **3b** gave a 2/7 mixture of **3a** and **3b**.[31] The equatorial

Scheme VI



Scheme VII



isomer **3a** could not be obtained as the major product from **3b**. Therefore, the predominant formation of **3a** from Gla was not the result of equilibrium e. Accordingly, paths b′, c′, and d were not likely, because they involved path e. Thus, pathways b or c appeared most likely.

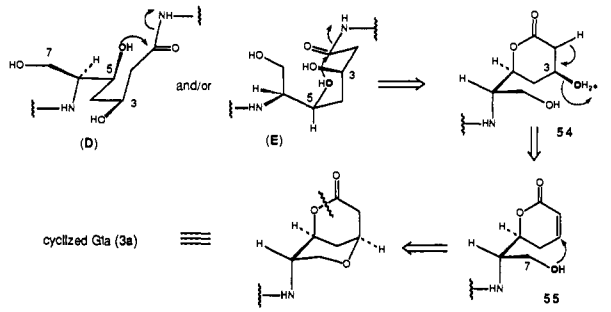
Examined next was an acidolysis of each of the *E* and *Z* α,β-unsaturated carboxylates, **46** and **47** (entries 6 and 7). The *E* isomer **46** gave a 2/1 mixture of **3a** and **3b**. This result was almost in accord with that of eq 4 and indicated that the cyclization did not occur from the *E* isomer. On the other hand, the *Z* isomer **47** showed high selectivity for the formation of the equatorial isomer **3a** (**3a**/**3b** = 9/1). This suggested pathway c to be the plausible one. However, pathway c as a means of affording **47** from Gla appeared unlikely, because it required stereoselective elimination of the C3 hydroxyl group to produce a *Z* C–C double bond; this process would require high energy in view of steric as well as stereoelectronic factors, when compared to the process that would afford the *E* isomer.

From the above results, we finally arrived at the conclusion that the cyclization involved a compound equivalent to **47** such as α,β-unsaturated δ-lactone **48**. In order to produce the unsaturated lactone intermediate **48**, δ-lactonization of Gla followed by elimination of the C3 hydroxyl group was the required process (Gla → **49** → **48**): subsequent intramolecular 1,4-addition of the C7 hydroxyl group in **48** would then give **3a**. Indeed, treatment of the lactone **48** gave a 10/1 mixture of **3a** and **3b**. The 3*S*-hydroxy lactone **49**, a synthetic intermediate of Gla, also gave an 11/1 mixture of **3a** and **3b**. Furthermore, the 3*R* epimer **50** provided the same mixture. Since both **49** and its epimer **50** provided a similar product ratio as **48**, elimination of the C3 hydroxyl group of Gla occurred after the formation of the δ-lactone **49**.

Experiments to determine whether the S_N1 substitution (b) occurred during the cyclization of Gla could not be performed. However, the mechanism involving the hypothetical lactone intermediate appeared to be more reasonable than b, and this is supported by the following examples. (1) The tetrol **51**, which possesses a hydroxymethyl group instead of the carboxyl group at C1, was found to be stable under the reaction conditions, resulting in complete recovery of the starting material. Therefore, the presence of a carboxyl group at C1 was necessary (lactonization from C5) for the cyclization of Gla. (2) C5 dehydroxyl compound **52** (a 1/1 mixture of diastereomers at C3),[32] which

(31) The reduced recovery yield (38%) would be the result of the decomposition of **3b**, probably due to a retro-aldol type reaction.

Scheme VIII



is not capable of forming the δ-lactone intermediate, provided a 4/3 mixture of **53a** and **53b** (Scheme VII). Although the mechanism of the cyclization of **52** could not be determined, it apparently did not cyclize by an initial δ-lactonization process. Since the stereoselectivity was extremely low in the above process, it supported the speculation that the cyclization of Gla proceeded via the δ-lactone intermediate **48**.

Characterization of the conformation of the Gla residue in galantin I proved to be difficult even by the use of spectroscopic methods. However, inspection of molecular models revealed that the C5 hydroxyl group of the Gla residue could occupy a proximal position with the C1 amide carbonyl group as shown in structures D and E (Scheme VIII). From either one of the conformers, the C5 hydroxyl group of the Gla residue would attack the C1 amide carbonyl group to form δ-lactone intermediate **54**. This, upon dehydration, would afford the unsaturated lactone **55**, which on cyclization involving the C7 hydroxyl group would give **3a**.

The cyclization process of the Gla residue of galantin I was simulated by the use of Gla and its analogues as models. Under the controlled degradation conditions of galantin I as reported by Shiba et al.[2a] (TFA/H_2O = 1/1, 50 °C, 7 days), the left-half peptide (Glm-D-Ala-L-A_2Pr-D-Orn (D-Lys)-OH) and the right-half peptide (both H-Gla-N^{β}-Me-L-A_2Pr-Gly-Spe and H-N^{β}-Me-L-A_2Pr-Gly-Spe) were isolated. The structure of the Gla residue, obtained from the peptide, was shown to be **3a**. This indicated that the peptide bond breaking occurred easily at both sides of the Gla residue: between D-Orn-OH and H-Gla, and between Gla-OH and H-N^{β}-Me-A_2Pr. In the latter case, the C5 hydroxyl group of Gla may participate with C1 to afford the δ-lactone **54**, which would then undergo dehydration to **55** followed by cyclization to **3a** (Scheme VIII).

Galantin I attracts further interest in view of its highly functionalized structure which could chelate with metals, carboxylates, etc. The polyamine structure in the right half of galantin I especially resembles those of neurotoxins such as JSTX and PTX, potent antagonists of the excitatory amino acid receptors in vertebrate and invertebrate central nervous systems.[33] The work is now being extended to such areas and will be reported in due course.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded on one of the following instruments: JEOL FX 100, JEOL JNM-EX 270, Nicolet NT-360, and GE GN-500. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$, C_6H_6 (δ = 7.32) in C_6D_6, or TSP (δ = 0.00) in D_2O. IR spectra were measured either on a Hitachi 270-30 or on a Perkin-Elmer FT-IR 1640 spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Hitachi M-80B spectrometer for secondary ionization mass spectrometry (SIMS) and electron-impact ionization (EI) or on a JEOL JMX-HX 110 for fast atom bombardment ionization (FAB). Optical rotations were taken on a Perkin-Elmer 241 polarimeter. All reactions

(32) Procedure for the synthesis of **52**: (1) **30**, $Ph_3PCHCHO$, benzene, room temperature, 17 h (45%); (2) H_2/10% Pd–C, ethyl acetate, room temperature, 14 h (84%); (3) *tert*-butyl acetate, lithium diisopropylamide, THF, –78 °C, 30 min (92%).

(33) PTX: Eldefrawi, A. T.; Eldefrawi, M. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Oltz, E.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4910. JSTX: Akaike, N.; Kawai, N.; Kiskin, N. I.; Kljuchko, E. M.; Krishtal, O. A.; Tsyndrenko, A. Y. *Neuroscience Lett.* **1987**, *79*, 326.

were monitored by thin-layer chromatography (TLC), which was performed with precoated TLC plates (Merck). Silica gel (Merck 60, 70–230 mesh) was used for column chromatography. Medium-pressure liquid chromatography (MPLC) was performed with a LiChroprep Si 60 Lobar column (Merck). Precoated TLC plates (Merck, silica gel 60F-254, layer thickness, 0.25 mm, or silica gel F-254, layer thickness, 0.5 mm) were used for preparative TLC. HPLC was performed with a UNISIL PACK 5C18 (GL Sciences, Tokyo). Yields are of chromatographically and spectroscopically (^{1}H NMR) pure materials, unless otherwise stated.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butoxycarbonyl)-N^{β}-methyl-L-α,β-diaminopropionic Acid [Z-N^{β}-Me-L-A_2Pr(Boc)-OH] (8c). To a solution of **6a** (1.0 g, 4.2 mmol) in tetrahydrofuran (THF) (5 mL) and H_2O (5 mL) were added triethylamine (0.7 mL, 5.02 mmol) and di-*tert*-butyl dicarbonate (Boc_2O) (1.5 mL, 6.53 mmol) at room temperature. After the mixture was stirred for 5 h, THF was removed in vacuo and the resulting aqueous suspension was washed with diethyl ether (Et_2O). The aqueous layer was acidified with 1 N aqueous HCl and extracted with ethyl acetate several times. The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo to give **6b** as an oil which, without further purification, was dissolved in Et_2O (5 mL). To this solution was added a solution of diazomethane in Et_2O at room temperature over 10 min. The solvent was removed under reduced pressure to give an oily residue. This was purified by column chromatography on silica gel (Et_2O/hexane, 1/2) to give the methyl ester of **6b** (Z-L-A_2Pr(Boc)-OMe, 1.48 g, 98% from **6a**). To a solution of Z-L-A_2Pr(Boc)-OMe (580 mg, 1.65 mmol) in methylene chloride (2 mL) was added trifluoroacetic acid (TFA) (2 mL) at room temperature. The mixture was stirred for 20 min and concentrated in vacuo. The residue was suspended in water (1 mL), and to this mixture were added, successively, cyclopentadiene (0.68 mL, 8.29 mmol) and 37% aqueous formaldehyde (0.37 mL, 4.94 mmol) at room temperature. The mixture was stirred vigorously for 1 h and washed with hexane. The aqueous layer was neutralized with 5% aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (chloroform, then methanol/chloroform, 1/49) to give **7** as a mixture of diastereomers (592 mg). To a solution of **7** in chloroform (8 mL) at 0 °C were added triethylsilane (0.79 mL, 4.95 mmol) and TFA (8 mL). The mixture was stirred for 14 h at room temperature. The resulting mixture was concentrated in vacuo, and the residue was dissolved in chloroform (2.8 mL), acidified with 2 N aqueous HCl (8 mL), and washed with 1/1 Et_2O/hexane. The aqueous layer was neutralized with 5% aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. This, upon column chromatography on silica gel (chloroform, then methanol/chloroform, 1/19), gave **8a** as an oil (344 mg). This was dissolved in methylene chloride (2 mL) and treated with Boc_2O (0.45 mL, 1.96 mmol) and Et_3N (0.018 mL, 0.13 mmol). After the solution was stirred for 2 h at room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1/2) to give **8b** as an oil (357 mg, 59% from **6b**): $[\alpha]^{25}_D$ +5.5° (*c* 0.8, $CHCl_3$); IR (neat) 3348, 2984, 1732, 1518, 1456, 1440, 1254, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.42 (s, 9 H), 2.84 (s, 3 H), 3.52 (m, 2 H), 3.75 (s, 3 H), 4.45 (m, 1 H), 5.08 (s, 2 H), 5.90 (br s, 1 H), 7.30 (s, 5 H); MS (SIMS) *m/z* 367 (M + H)$^+$, 267, 233. Anal. Calcd for $C_{18}H_{26}O_6N_2$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.77; H, 7.26; N, 7.72. To a solution of Z-N^{β}-Me-L-A_2Pr(Boc)-OMe (**8b**) (222 mg, 0.63 mmol) in THF (1.5 mL) was added 1 N aqueous NaOH (0.76 mL, 0.76 mmol) at 0 °C. After being stirred for 14 h at the same temperature, the reaction mixture was quenched with 1 N aqueous HCl and extracted with ethyl acetate several times. The combined extract was dried ($MgSO_4$) and concentrated in vacuo to give **8c** as an oil. This, without further purification, was subjected to a peptide coupling reaction.

***N*-(Benzyloxycarbonyl)glycyl-N^4-(*tert*-butoxycarbonyl)putrescine (10a).** To a solution of putrescine (0.17 g, 1.93 mmol) in *N*,*N*-dimethylformamide (DMF) (30 mL) at 80 °C was added a solution of *N*-(benzyloxycarbonyl)glycine succinimido ester (Z-Gly-OSu) (0.3 g, 0.98 mmol) in DMF (20 mL) over a period of 2 min. After being stirred for 10 min at the same temperature, the solution was cooled to room temperature, and to this solution were added Et_3N (0.5 mL, 3.59 mmol) and Boc_2O (0.8 mL, 3.48 mmol). After being stirred for 4 h, the solution was acidified with 1 N aqueous HCl and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O, ethyl acetate, then methanol/chloroform, 3/197) to give **10a** as colorless crystals (184 mg, 50%): mp 88–89 °C; IR (neat) 3332, 2940, 1694, 1534, 1368, 1250, 1170, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.43 (s, 9 H), 1.40–1.60 (m, 4 H), 3.18 (m, 4 H), 3.84 (d, 2 H, *J* = 6 Hz), 4.64 (br s, 1 H), 5.12 (s, 2 H), 5.62 (br s, 1 H), 6.39 (br s, 1 H), 7.33 (s, 5 H); MS (SIMS) *m/z* 380 (M + H)$^+$, 280. Anal. Calcd for $C_{19}H_{29}O_5N_3$: C, 60.14; H, 7.70; N, 11.07. Found: C, 59.91; H, 7.80; N, 11.06.

***N*-(Benzyloxycarbonyl)glycyl-N^5,N^8-bis(*tert*-butoxycarbonyl)spermidine [Z-Gly-N^5,N^8-di-Boc-Spe(4,3)] (11b).** A solution of **10a** (530 mg, 1.40 mmol) in methylene chloride (2 mL) and TFA (2 mL) was stirred for 20 min at room temperature. The solution was concentrated in vacuo to give **10b** as a TFA salt. This was dissolved in methanol (5 mL), and the pH of the solution was adjusted to 8 by the addition of Et_3N. To this were added, successively, a solution of sodium cyanoborohydride (88 mg, 1.40 mmol) in methanol (0.5 mL) and a solution of *N*-(*tert*-butoxycarbonyl)-3-aminopropanal (300 mg, 1.73 mmol) in methanol (1.5 mL). The resulting solution was stirred for 13 h at room temperature. The solution was quenched with water, and then the methanol was evaporated under reduced pressure. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo to give **11a** as an oily residue. This was dissolved in dioxane (5 mL) along with Et_3N (0.25 mL, 1.79 mmol) and Boc_2O (0.4 mL, 1.74 mmol). The mixture was stirred for 3 h at room temperature and was then concentrated in vacuo. The residue was purified, successively, by silica gel column chromatography (methanol/chloroform, 1/49) and by MPLC (methanol/chloroform, 1/49) to give **11b** as an oil (517 mg, 69% from **10a**): IR (neat) 3340, 2984, 1682, 1530, 1482, 1422, 1368, 1250, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.43 (s, 9 H), 1.45 (s, 9 H), 1.20–2.12 (m, 6 H), 3.16 (m, 8 H), 3.84 (d, 2 H, *J* = 6 Hz), 4.90 (br s, 1 H), 5.11 (s, 2 H), 5.76 (br s, 1 H), 6.50 (br s, 1 H), 7.32 (s, 5 H); MS (SIMS) *m/z* 537 (M + H)$^+$, 437. Anal. Calcd for $C_{27}H_{44}O_7N_4$: C, 60.42; H, 8.26; N, 10.44. Found: C, 60.19; H, 8.47; N, 10.37.

(5*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-6-amino-5,7-(isopropylidenedioxy)-2(*E*)-hepten-1-ol (13). To a solution of **12** (1.51 g, 4.03 mmol) in acetone (5 mL) and 2,2-dimethoxypropane (5 mL) was added *dl*-10-camphorsulfonic acid (CSA) (10 mg) at room temperature. The reaction mixture was stirred for 3 h at room temperature. After the addition of $NaHCO_3$ powder (30 mg) to this mixture, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1/9) to give the TBS ether of **13** as an oil (1.36 g, 82%). To a solution of the TBS ether (1.36 g, 3.28 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (*n*-Bu_4NF, 1 M solution in THF) (3.3 mL, 3.3 mmol) at room temperature. The reaction mixture was stirred for 1 h, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a crude residue which, upon purification by column chromatography on silica gel (Et_2O/hexane, 1/1, then Et_2O), gave **13** (759 mg, 77%) as an oil: $[\alpha]^{25}_D$ +11.3° (*c* 0.72, $CHCl_3$); IR (neat) 3476, 2988, 1716, 1504, 1370, 1244, 1168, 1088, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.40 (s, 3 H), 1.45 (s, 12 H), 1.63 (br s, 1 H), 2.23 (m, 2 H), 3.53 (dq, 1 H, *J* = 2, 10 Hz), 3.73 (dd, 1 H, *J* = 2, 12 Hz), 3.98 (dt, 1 H, *J* = 2, 7 Hz), 4.0–4.16 (m, 3 H), 5.33 (br d, 1 H, *J* = 10 Hz), 5.62 (dt, 1 H, *J* = 7, 15 Hz), 5.72 (dt, 1 H, *J* = 6, 15 Hz); MS (SIMS) *m/z* 302 (M + H)$^+$, 202. Anal. Calcd for $C_{15}H_{27}O_5N$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.99; H, 9.28; N, 4.61.

(3*R*,5*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-6-amino-3-hydroxy-5,7-(isopropylidenedioxy)-1-heptanol (14a) and Its 3*S* Isomer (14b). To a solution of **13** (759 mg, 2.52 mmol) in methylene chloride (5 mL) was added 3-chloroperbenzoic acid (MCPBA) (653 mg, 3.03 mmol) at 0 °C under N_2. The resulting suspension was stirred for 1 h at the same temperature. The reaction mixture was quenched with 5% aqueous K_2CO_3 and extracted with chloroform and then ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an oily residue which, upon purification by column chromatography on silica gel (Et_2O/hexane, 1/1, then Et_2O), gave a diastereomeric mixture of 2,3-epoxy alcohols (784 mg, 98%). To a suspension of $LiAlH_4$ (140 mg, 3.69 mmol) in Et_2O (5 mL) was added a solution of the epoxide (764 mg, 2.41 mmol) in Et_2O (7 mL), drop by drop, at 0 °C. The reaction mixture was vigorously stirred for 1 h at 0 °C and then 30 min at room temperature. The resulting mixture was diluted with Et_2O (50 mL) at 0 °C and quenched by adding ice tips, portion by portion. After the suspension was stirred for 10 min at room temperature, to it was added $MgSO_4$ powder. The suspension was stirred for 10 min and filtered. The filtrate was concentrated in vacuo to give an oily residue. This, upon purification by column chromatography on silica gel (methanol/chloroform, 1/49, then 1/9) and MPLC (methanol/chloroform, 1/49, then 1/9), gave a mixture of **14b** (187 mg, 24%) and an inseparable mixture of **14a** and a 1,2-dihydroxy compound (255 mg). In order to perform an isolation of **14a** from the mixture, this was first converted to the corresponding *tert*-butyldimethylsilyl (TBS) ether. The resulting mixture was separated by column chromatography on silica gel to give the TBS ether of **14a**. The TBS group of this compound was removed with *n*-Bu_4NF to give **14a**. These transformations are described as fol-

lows: The mixture of **14a** and the 1,2-dihydroxy compound (255 mg) was dissolved in DMF (3 mL) along with imidazole (109 mg, 1.60 mmol). To this solution was added a solution of *tert*-butyldimethylsilyl chloride (133 mg, 0.88 mmol) in DMF (2 mL) at 0 °C. The solution was stirred for 3 h under N_2 and poured into water. This was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O/hexane, 3/7, then Et_2O) and MPLC (Et_2O/hexane, 3.7, then 1/1) to give the TBS ether of **14a** (120 mg) and the TBS ether of the 1,2-diol (147 mg). To a solution of the TBS ether of **14a** (120 mg, 0.28 mmol) in THF (0.5 mL) was added *n*-Bu_4NF (1 M solution in THF, 335 μL, 0.34 mmol) at room temperature. After being stirred for 1 h, the mixture was quenched with aqueous NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (methanol/chloroform, 3/97) gave **14a** (101 mg, 13% from **13**) as an oil: $[\alpha]^{25}_D$ −17.0° (*c* 1.03, $CHCl_3$); IR (neat) 3468, 2984, 2944, 1698, 1506, 1458, 1278, 1246, 1126, 1086, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3 H), 1.43 (s, 9 H), 1.45 (s, 3 H), 1.40–1.80 (m, 4 H), 2.80 (m, 1 H), 3.53 (ddd, 1 H, *J* = 2, 2, 10 Hz), 3.68 (dd, 1 H, *J* = 2, 12 Hz), 3.81 (t, 2 H, *J* = 5 Hz), 4.10 (dd, 1 H, *J* = 2, 12 Hz), 4.22 (dt, 1 H, *J* = 2, 6 Hz), 3.40–4.32 (m, 2 H), 5.39 (d, 1 H, *J* = 10 Hz); MS (SIMS) *m/z* 320 $(M + H)^+$, 220. Anal. Calcd for $C_{15}H_{29}O_6N$: C, 56.40; H, 9.15; N, 4.39. Found: C, 56.31; H, 9.42; N, 4.51. **14b**: oil; $[\alpha]^{25}_D$ +3.6° (*c* 1.13, $CHCl_3$); IR (neat) 3472, 2988, 2948, 1696, 1504, 1386, 1370, 1272, 1246, 1200, 1170, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40 (s, 3 H), 1.46 (s, 9 H), 1.51 (s, 3 H), 1.50–1.94 (m, 4 H), 2.70 (br s, 1 H), 3.36 (m, 1 H), 3.74 (dd, 1 H, *J* = 2, 12 Hz), 3.70–3.92 (m, 2 H), 4.12 (dd, 1 H, *J* = 2, 12 Hz), 3.94–4.39 (m, 1 H), 4.28 (ddd, 1 H, *J* = 2, 6, 7 Hz), 5.34 (d, 1 H, *J* = 10 Hz); MS (SIMS) *m/z* 320 $(M + H)^+$, 220. Anal. Calcd for $C_{15}H_{29}O_6N$: C, 56.40; H, 9.15; N, 4.39. Found: C, 56.01; H, 9.39; N, 4.39.

Methyl (3*R*,5*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-6-amino-7-[(*tert*-butyldimethylsilyl)oxy]-3,5-(isopropylidenedioxy)heptanoate (18). A suspension of PtO_2 (66 mg, 0.29 mmol) in water (1 mL) was reduced primarily with H_2 (1 atm) for 1 h at room temperature. Oxygen was passed through the suspension, and to this was added a solution of **14b** (93 mg, 0.29 mmol) in dioxane (2 mL). The reaction mixture was vigorously stirred for 7 h at 45 °C and 14 h at room temperature under O_2 (1 atm). The suspension was filtered, and the filtrate was concentrated in vacuo to give an oily residue. This, upon treatment with diazomethane in Et_2O followed by purification with preparative TLC (Et_2O), gave an ester (50 mg, 50%). To a solution of the ester (16.5 mg, 0.05 mmol) in methanol (0.5 mL) was added CSA (1.5 mg) at room temperature. After being stirred for 14 h under N_2, the reaction was quenched with $NaHCO_3$ powder. The suspension was concentrated in vacuo to give a crude residue which, upon purification by column chromatography on silica gel (methanol/chloroform, 1/49, then 1/9), gave an oily residue (10 mg, 69%). This (10 mg, 0.03 mmol) was dissolved in methylene chloride (0.5 mL) along with Et_3N (9 μL, 0.06 mmol). To this solution was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (9 μL, 0.04 mmol) at 0 °C. The solution was stirred for 10 min at 0 °C under N_2 and quenched with aqueous NH_4Cl. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (methanol/chloroform, 1/49, then 1/9) to give primary silyl ether (8 mg, 58%). To a solution (0.2 mL) of the silyl ether (8 mg, 0.02 mmol) in benzene (0.2 mL) were added 2,2-dimethoxypropane (0.2 mL) and CSA (1 mg) at room temperature. The mixture was stirred for 10 min and quenched with aqueous $NaHCO_3$. The solution was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O/hexane, 3/7) to give **18** (5.7 mg, 65%) as an oil: $[\alpha]^{25}_D$ +12.7° (*c* 1.2, $CHCl_3$); IR (neat) 3476, 2960, 1724, 1496, 1258, 1168, 1114, 1026 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.98 (s, 9 H), 1.05 (ddd, 1 H, *J* = 2.5, 2.5, 13 Hz, 4α-H), 1.33 (s, 3 H, acetonide β-Me), 1.35 (s, 3 H, acetonide α-Me), 1.48 (s, 9 H), 1.51 (ddd, 1 H, *J* = 13, 13, 13 Hz, 4β-H), 2.06 (dd, 1 H, *J* = 4.5, 11 Hz, 2-H), 2.42 (dd, 1 H, *J* = 8.5, 11 Hz, 2-H), 3.31 (s, 3 H), 3.63 (dd, 1 H, *J* = 9, 9 Hz, 7-H), 3.76 (dd, 1 H, *J* = 5.5, 9 Hz, 7-H), 3.92 (m, 1 H, 6-H), 4.23 (ddd, 1 H, *J* = 2.5, 2.5, 13.0 Hz, 5-H), 4.27 (dddd, 1 H, *J* = 2.5, 4.5, 8.5, 13 Hz, 3-H), 4.95 (d, 1 H, *J* = 9 Hz, NH), each 9.6% of NOE (300 MHz, C_6D_6) was observed between the α-Me (δ 1.35) and 3-H, and α-Me and 5-H; MS (FAB) *m/z* 462 $(M)^+$; HRMS (FAB) *m/z* calcd for $C_{22}H_{44}O_7NSi$ $(M + H)^+$ 462.2887, found 462.2888.

(3*R*,5*S*,6*S*)-*N*-(Benzyloxycarbonyl)-1,3-diacetoxy-6-amino-5,7-(isopropylidenedioxy)heptane (16a). A solution of **14a** (100 mg, 0.31 mmol) in acetic anhydride (1 mL) and pyridine (1 mL) was stirred for 14 h at room temperature. The reaction was concentrated in vacuo to give a crude residue which, upon purification by column chromatography on silica gel (Et_2O/hexane, 1/1, then Et_2O), gave **15a** (99 mg, 78%). To a solution of **15a** (99 mg, 0.25 mmol) in methylene chloride (1 mL) were added, successively, 2,6-lutidine (60 μL, 0.52 mmol) and TBSOTf (115 μL, 0.50 mmol) at room temperature. The solution was stirred for 30 min under N_2 and quenched with aqueous NH_4Cl. The solution was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give an oily residue. The residue was dissolved in THF (0.5 mL), and to this were added, successively, benzyl bromide (60 μL, 0.50 mmol) and *n*-Bu_4NF (1 M solution in THF) (295 μL, 0.30 mmol) at 0 °C under N_2. The mixture was stirred for 1 h at the same temperature and quenched with aqueous NH_4Cl. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (Et_2O/hexane, 1/1) gave **16a** (81 mg, 75%) as an oil: $[\alpha]^{25}_D$ +5.0° (*c* 1.4, $CHCl_3$); IR (neat) 3360, 2996, 1740, 1514, 1374, 1234, 1086, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3 H), 1.38 (s, 3 H), 1.56–2.12 (m, 4 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 3.51 (ddd, 1 H, *J* = 2, 2, 10 Hz), 3.72 (dd, 1 H, *J* = 2, 12 Hz), 3.98 (dd, 1 H, *J* = 1.5, 10 Hz), 4.05 (t, 2 H, *J* = 6 Hz), 5.10 (s, 2 H), 5.12 (quintet, 1 H, *J* = 6 Hz), 5.52 (br d, 1 H, *J* = 10 Hz), 7.34 (s, 5 H); MS (EI) *m/z* 437 M^+; HRMS (EI) *m/z* calcd for $C_{22}H_{31}O_8N$ (M^+) 437.2048, found 437.2089.

(3*S*,5*S*,6*S*)-*N*-(Benzyloxycarbonyl)-1,3-diacetoxy-6-amino-5,7-(isopropylidenedioxy)heptane (16b). In a manner similar to that used for the preparation of **16a**, **16b** (160 mg, 73%) was obtained from **14b** (160 mg, 0.50 mmol): $[\alpha]^{25}_D$ −5.5° (*c* 1.0, $CHCl_3$); IR (neat) 2968, 1742, 1512, 1376, 1236, 1084, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35 (s, 3 H), 1.42 (s, 3 H), 1.60–2.08 (m, 4 H), 2.02 (s, 3 H), 2.03 (s, 3 H), 3.60 (ddd, 1 H, *J* = 2, 2, 10 Hz), 3.72 (dd, 1 H, *J* = 2, 12 Hz), 3.98 (dd, 1 H, *J* = 1.5, 10 Hz), 4.05 (m, 2 H), 5.09 (s, 2 H), 5.17 (quintet, 1 H, *J* = 6 Hz), 5.52 (br d, 1 H, *J* = 10 Hz), 7.34 (s, 5 H); MS (EI) *m/z* 437 M^+; HRMS (EI) *m/z* calcd for $C_{22}H_{31}O_8N$ (M^+) 437.2048, found 437.2068.

***N*-(Benzyloxycarbonyl)-5,7-isopropylidenegalantinic Acid (19a).** A solution of **16a** (81 mg, 0.18 mmol) and K_2CO_3 (1 mg) in methanol (1 mL) was stirred for 3 h at room temperature under N_2. The reaction was quenched with aqueous NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo to give an oily residue. Purification of the residue by column chromatography on silica gel (chloroform, then methanol/chloroform, 1/24) gave diol **17a** (65 mg, 100%) as an oil. To a suspension of PtO_2 (66 mg, 0.29 mmol) (pretreated with H_2 (1 atm) for 1 h at room temperature) in H_2O (1 mL) under O_2 (1 atm) was added a solution of **17a** (65 mg, 0.18 mmol) in dioxane (2 mL). The suspension was vigorously stirred for 3 h at 45 °C and then 20 h at room temperature. The mixture was filtered through glass filter filled with Celite, and the filtrate was concentrated in vacuo to give **19a** (59 mg, 83%) as an oil; spectroscopic data and physical constants of **19a** were measured by the use of its methyl ester (prepared by the esterification with diazomethane). Methyl ester of **19a**: oil; $[\alpha]^{25}_D$ +6.5° (*c* 0.6, $CHCl_3$); IR (neat) 3460, 2960, 1730, 1514, 1386, 1278, 1224, 1198, 1150, 1086, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3 H), 1.48 (s, 3 H), 1.20–1.68 (m, 2 H), 2.44 (d, 2 H, *J* = 6 Hz), 3.19 (d, 1 H, *J* = 5 Hz), 3.58 (ddd, 1 H, *J* = 2, 2, 10 Hz), 3.71 (s, 3 H), 3.74 (dd, 1 H, *J* = 2, 12 Hz), 3.96–4.40 (m, 3 H), 5.11 (s, 2 H), 5.55 (br d, 1 H, *J* = 10 Hz), 7.36 (s, 5 H); MS (EI) *m/z* 381 M^+; HRMS (EI) *m/z* calcd for $C_{19}H_{27}O_7N$ (M^+) 381.1785, found 381.1806.

3-*epi*-*N*-(Benzyloxycarbonyl)-5,7-isopropylidenegalantinic Acid (19b). In a manner similar to that used for the preparation of **19a**, diacetate **16b** (76 mg, 0.17 mmol) was hydrolyzed to **17b** (100%), which was oxidized with PtO_2 to give **19b** (60 mg, 96%) as an oil; spectroscopic data and physical constants of **19b** were measured by the use of its methyl ester. Methyl ester of **19b**: oil; $[\alpha]^{25}_D$ +14.2° (*c* 0.48, $CHCl_3$); IR (neat) 3468, 2996, 2960, 1724, 1514, 1456, 1440, 1386, 1332, 1276, 1216, 1202, 1176, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.39 (s, 3 H), 1.51 (s, 3 H), 1.18–1.82 (m, 2 H), 2.43 (m, 2 H), 3.34 (d, 1 H, *J* = 3 Hz), 3.62 (m, 1 H), 3.72 (s, 3 H), 3.76 (dd, 1 H, *J* = 2, 10 Hz), 4.13 (dd, 1 H, *J* = 2, 12 Hz), 3.98–4.46 (m, 2 H), 5.11 (s, 2 H), 5.54 (br d, 1 H, *J* = 10 Hz), 7.38 (s, 5 H); MS (EI) *m/z* 381 M^+; HRMS (EI) *m/z* calcd for $C_{19}H_{27}O_7N$ (M^+) 381.1785, found 381.1768.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butoxycarbonyl)-L-α,β-diaminopropionyl-N^{δ}-(*tert*-butoxycarbonyl)-D-ornithine Methyl Ester [Z-L-A_2Pr(Boc)-D-Orn(Boc)-OMe] (21). A solution of N^{α}-Z-N^{δ}-Boc-D-Orn-OMe (290 mg, 0.76 mmol) in methanol (2 mL) was stirred over 10% palladium on carbon (10 mg) under H_2 (1 atm) for 14 h at room temperature. The suspension was filtered through Celite and concentrated in vacuo. The residue was dissolved in methylene chloride (5 mL) along with **6b** [prepared by the hydrolysis of the methyl ester of **6b** (222 mg, 0.63 mmol), 1 N NaOH, room temperature, 0 °C, 14 h; 100%] and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC) (181 mg, 0.94 mmol). The solution was stirred for 2.5 h at room temperature under N_2, quenched with water, and extracted with ethyl acetate. The organic phase was washed, successively, with 1 N HCl, brine,

saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue. This, upon purification with column chromatography on silica gel (methanol/chloroform, 1/99), gave **21** as colorless crystals (294 mg, 82%): mp 141–142 °C; $[\alpha]^{25}_D$ −23.9° (*c* 1.25, $CHCl_3$); IR (neat) 3348, 2984, 1744, 1692, 1662, 1536, 1270, 1172, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.41 (s, 18 H), 1.41–2.10 (m, 4 H), 3.07 (m, 2 H), 3.49 (t, 2 H, *J* = 6 Hz), 3.70 (s, 3 H), 4.27 (dt, 1 H, *J* = 6, 6 Hz), 4.4–4.8 (m, 2 H), 5.11 (s, 2 H), 5.20 (br d, 1 H, *J* = 8 Hz), 6.23 (br s, 1 H), 7.10 (br d, 1 H, *J* = 6 Hz), 7.32 (s, 5 H); MS (SIMS) *m/z* 567 $(M + H)^+$, 467, 367. Anal. Calcd for $C_{27}H_{42}O_9N_4$: C, 57.23; H, 7.47; N, 9.89. Found: C, 56.90; H, 7.52; N, 9.83.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butoxycarbonyl)-L-α,β-diaminopropionyl-N^{ϵ}-(*tert*-butoxycarbonyl)-D-lysine Methyl Ester [Z-L-A_2Pr(Boc)-D-Lys(Boc)-OMe]. In a manner similar to that used to prepare **21**, the title compound (91 mg, 85%) was prepared by the coupling of **6b** (65 mg, 0.18 mmol) with H-N^{ϵ}-Boc-D-Lys-OMe (88 mg, 0.22 mmol): colorless crystals, mp 141–142.5 °C; $[\alpha]^{25}_D$ −21.8° (*c* 1.52, $CHCl_3$); IR (neat) 3348, 2984, 1696, 1532, 1252, 1170, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.48 (s, 18 H), 1.12–2.00 (m, 6 H), 3.10 (m, 2 H), 3.54 (t, 2 H, *J* = 6 Hz), 3.76 (s, 3 H), 4.32 (m, 1 H), 4.40–4.92 (m, 2 H), 5.16 (s, 2 H), 5.14 (m, 1 H), 6.24 (br s, 1 H), 7.00 (br d, 1 H, *J* = 6 Hz), 7.37 (s, 5 H); MS (SIMS) *m/z* 581 $(M + H)^+$, 481, 381. Anal. Calcd for $C_{28}H_{44}O_9N_4$: C, 57.91; H, 7.64; N, 9.65. Found: C, 57.61; H, 7.74; N, 9.59.

N-(Benzyloxycarbonyl)-D-alanyl-N^{β}-(*tert*-butoxycarbonyl)-L-α,β-diaminopropionyl-N^{δ}-(*tert*-butoxycarbonyl)-D-ornithine Methyl Ester [Z-D-Ala-L-A_2Pr(Boc)-D-Orn(Boc)-OMe] (22). A solution of **21** (319 mg, 0.56 mmol) in methanol (5 mL) was stirred over 10% palladium on carbon (16 mg) under H_2 (1 atm) for 17 h at room temperature. The suspension was filtered through Celite, concentrated in vacuo, and purified by column chromatography on silica gel (methanol/chloroform, 1/9, then 1/4) to give pure amine (241 mg, 99%). This material (241 mg, 0.56 mmol) was dissolved in methylene chloride (5 mL) along with *N*-Z-D-alanine (150 mg, 0.67 mmol) and WSC (160 mg, 0.83 mmol). The reaction mixture was stirred for 1.5 h at room temperature under N_2, quenched with brine, and extracted with ethyl acetate. The organic layer was washed with 1 N aqueous HCl, brine, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentraed in vacuo. The residue was purified by column chromatography on silica gel (methanol/chloroform, 1/50) to give **22** (312 mg, 88%) as colorless crystals: mp 171–172 °C; $[\alpha]^{25}_D$ −31.4° (*c* 1.18, $CHCl_3$); IR (neat) 3336, 2984, 1700, 1532, 1254, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40 (d, 3 H, *J* = 8 Hz), 1.41 (s, 9 H), 1.45 (s, 9 H), 1.45–2.10 (m, 4 H), 3.08 (q, 2 H, *J* = 7 Hz), 3.56 (t, 2 H, *J* = Hz), 3.70 (s, 3 H), 4.10 (dq, 1 H, *J* = 7, 7 Hz), 4.20–4.64 (m, 3 H), 4.88 (m, 1 H), 5.01 (d, 1 H, *J* = 12 Hz), 5.12 (d, 1 H, *J* = 12 Hz), 5.44 (s, 1 H), 7.32 (s, 5 H), 7.40 (s, 1 H), 7.80 (s, 1 H); MS (SIMS) *m/z* 638 $(M + H)^+$, 538, 438. Anal. Calcd for $C_{30}H_{47}O_{10}N_5$: C, 56.50; H, 7.43; N, 10.98. Found: C, 56.34; H, 7.37; N, 10.91.

N-(Benzyloxycarbonyl)-D-alanyl-N^{β}-(*tert*-butoxycarbonyl)-L-α,β-diaminopropionyl-N^{ϵ}-(*tert*-butoxycarbonyl)-D-lysine Methyl Ester [Z-D-Ala-L-A_2Pr(Boc)-D-Lys(Boc)-OMe]. The title compound (73 mg, 71%) was obtained by the coupling of *N*-Z-D-alanine (42 mg, 0.19 mmol) with Z-L-A_2Pr(Boc)-D-Lys(Boc)-OMe (91 mg, 0.16 mmol) according to a procedure similar to that of **22**: colorless crystals, mp 136–138 °C; $[\alpha]^{25}_D$ −29.7° (*c* 1.0, $CHCl_3$); IR (neat) 3324, 2984, 1698, 1524, 1252, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40 (d, 3 H, *J* = 8 Hz), 1.42 (s, 9 H), 1.43 (s, 9 H), 1.04–1.92 (m, 6 H), 3.04 (m, 2 H), 3.51 (br t, 2 H, *J* = 6 Hz), 3.68 (s, 3 H), 4.08 (m, 1 H), 4.47 (m, 2 H), 5.06 (m, 2 H), 5.16 (m, 1 H), 5.50 (br t, 1 H, *J* = 6 Hz), 5.86 (br s, 1 H), 7.30 (s, 5 H), 7.40 (s, 1 H), 7.90 (s, 1 H); MS (SIMS) *m/z* 652 $(M + H)^+$, 552, 452. Anal. Calcd for $C_{31}H_{49}O_{10}N_5$: C, 57.13; H, 7.58; N, 10.75. Found: C, 56.97; H, 7.63; N, 10.74.

Protected Galantinamic Acid (23b). To a solution of **23a** (99 mg, 0.20 mmol)[3] in acetone (1 mL) and 2,2-dimethoxypropane (1 mL) was added *dl*-10-camphorsulfonic acid (CSA) (2 mg). The reaction mixture was stirred for 20 h at room temperature and quenched with $NaHCO_3$ powder. The suspension was concentrated in vacuo to give an oily residue, which was purified by column chromatography on silica gel (Et_2O/hexane, 2/3) to give the methyl ester of **23b** (96 mg, 90%) as an oil: $[\alpha]^{25}_D$ −3.40° (*c* 1.46, $CHCl_3$); IR (neat) 2988, 1698, 1390, 1252, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40, 1.42 (each s, 30 H), 1.12–2.08 (m, 8 H), 3.08 (m, 2 H), 3.75 (s, 3 H), 4.0–4.4 (m, 4 H), 4.6 (br s, 1 H); MS (SIMS) *m/z* 545 $(M + H)^+$, 445, 345. Anal. Calcd for $C_{27}H_{48}O_9N_2$: C, 59.54; H, 8.88; N, 5.14. Found: C, 59.41; H, 9.17; N, 5.23. To a solution of the methyl ester of **23b** (142 mg, 0.26 mmol) in THF (0.63 mL) at 0 °C was added 1 N aqueous NaOH (315 μL, 0.32 mmol). The solution was stirred for 14 h at 0 °C and acidified with 1 N aqueous HCl. This was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo to give **23b** (140 mg, 100%). This was immediately subjected to the following coupling reaction.

Synthesis of the Left Half of Galantin I (Orn) (24a). A solution of **22** (248 mg, 0.39 mmol) in methanol (4 mL) was stirred over 10% palladium on carbon (10 mg) under H_2 (1 atm) for 14 h at room temperature. The suspension was filtered through Celite and concentrated in vacuo to give the corresponding amine as an oil. This was dissolved in DMF (3.5 mL) along with **23b** (140 mg, 0.26 mmol). To this mixture was added a solution of diphenylphosphoryl azide (DPPA) (85 μL, 0.39 mmol) in DMF (0.5 mL) and Et_3N (55 μL, 0.39 mmol) at 0 °C under N_2. The solution was stirred for 24 h at the same temperature. After dilution of the reaction mixture with ethyl acetate, the solution was washed with 1 N aqueous HCl, brine, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue. This, upon purification by column chromatography on silica gel (Et_2O) and MPLC (methanol/chloroform, 1/99), gave tetrapeptide **24a** (180 mg, 68%) as an amorphous solid: $[\alpha]^{25}_D$ −17.3° (*c* 0.9, $CHCl_3$); IR (neat) 3356, 2988, 2944, 1696, 1524, 1456, 1394, 1370, 1252, 1214, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42, 1.44, 1.47, 1.50 (each s, 51 H), 1.30–2.18 (m, 12 H), 3.10 (m, 4 H), 3.56 (m, 2 H), 3.72 (s, 3 H), 3.78 (br s, 0.5 H), 398 (br s, 0.5 H), 4.04 (m, 1 H), 4.08–4.30 (m, 3 H), 4.41 (m, 1 H), 4.51 (m, 1 H), 4.66 (br s, 0.5 H), 4.85 (br s, 1 H), 4.89 (br s, 0.5 H), 5.23 (br s, 1 H), 6.98 (br s, 1 H), 7.35 (br s, 1 H), 7.77 (br s, 1 H); MS (SIMS) *m/z* 1022 $(M + Li)^+$, 1016 $(M + H)^+$, 916; HRMS (FAB) *m/z* calcd for $C_{48}H_{86}O_{16}N_7$ $(M + H)^+$ 1016.6130, found 1016.6120.

Synthesis of the Left Half of Galantin I (Lys) (Methyl Ester of 24c). The title compound (106 mg, 67%) was obtained by the coupling of **23b** (84 mg, 0.15 mmol) with Z-D-Ala-L-A_2Pr(Boc)-D-Lys(Boc)-OMe (151 mg, 0.23 mmol) according to a procedure similar to that of **24a**. Methyl ester of **24c**: amorphous solid; $[\alpha]^{25}_D$ −15.1° (*c* 0.8, $CHCl_3$); IR (neat) 3356, 2984, 2940, 1696, 1516, 1456, 1394, 1370, 1250, 1214, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.43 (s, 51 H), 1.16–2.40 (m, 14 H), 3.08 (m, 4 H), 3.53 (m, 2 H), 3.71 (s, 3 H), 3.80–4.60 (m, 7 H), 4.90 (br s, 2 H), 5.20 (br s, 1 H), 6.96 (br s, 1 H), 7.28 (br s, 1 H), 7.76 (br s, 1 H); MS (SIMS) *m/z* 1036 $(M + Li)^+$, 1030 $(M + H)^+$, 930; HRMS (FAB) *m/z* calcd for $C_{49}H_{88}O_{16}N_7$ $(M + H)^+$ 1030.6287, found 1030.6300.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butoxycarbonyl)-N^{β}-methyl-L-α,β-diaminopropionylglycyl-N^5,N^8-bis(*tert*-butoxycarbonyl)spermidine [Z-N^{β}-Me-L-A_2Pr(Boc)-Gly-N^5,N^8-di-Boc-Spe(4,3)] (25). A solution of **11b** (185 mg, 0.34 mmol) in methanol (2 mL) was stirred over 10% palladium on carbon (13 mg) under H_2 (1 atm) for 14 h at room temperature. The suspension was filtered through Celite and concentrated in vacuo to give an oily residue which, upon purification by column chromatography on silica gel (methanol/chloroform, 1/9, then 1/4), gave pure amine (126 mg, 91%). This was dissolved in DMF (2 mL) along with **8c** [prepared by the hydrolysis of Z-N^{β}-Me-L-A_2Pr(Boc)-OMe **8b** (113 mg, 0.32 mmol); 0.5 N NaOH, 0 °C, 6 h; 100%]. To this solution was added a solution of diethyl phosphorocyanidate (DEPC) (73 μL, 0.48 mmol) in DMF (0.2 mL) and Et_3N (67 μL, 0.48 mmol) at 0 °C under N_2. After being stirred for 4 h at the same temperature, the solution was diluted with ethyl acetate and washed with 1 N aqueous HCl, brine, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/chloroform, 1/49) to give **25** (144 mg, 62%) as an amorphous solid: $[\alpha]^{25}_D$ −4.6° (*c* 0.94, $CHCl_3$); IR (neat) 3336, 2984, 1696, 1520, 1370, 1250, 1170, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.42, 1.43 (each s, 27 H), 1.20–1.84 (m, 6 H), 2.86 (s, 3 H), 2.90–3.40 (m, 8 H), 3.44–4.40 (m, 6 H), 5.00 (br s, 1 H), 5.08 (s, 2 H), 6.40–7.40 (each s, 2 H), 7.30 (s, 5 H); MS (SIMS) *m/z* 743 $(M + Li)^+$, 637, 537. Anal. Calcd for $C_{36}H_{60}O_{10}N_6$: C, 58.68; H, 8.21; N, 11.40. Found: C, 58.38; H, 8.13; N, 11.32.

N-(Benzyloxycarbonyl)-5,7-isopropylidenegalantinyl-N^{β}-(*tert*-butoxycarbonyl)-N^{β}-methyl-L-α,β-diaminopropionylglycyl-N^5,N^8-bis(*tert*-butoxycarbonyl)spermidine [Z-Gla-N^{β}-Me-L-A_2Pr(Boc)-Gly-N^5,N^8-di-Boc-Spe(4,3)] (26a). A solution of **25** (89 mg, 0.12 mmol) in methanol (2 mL) was stirred over 10% palladium on carbon (5 mg) under H_2 (1 atm) for 14 h at room temperature. The suspension was filtered through Celite and concentrated in vacuo to give an oily residue which, upon purification by column chromatography on silica gel (methanol/chloroform, 1/49, then 1/9) gave pure amine (72 mg, 99%). The amine (50 mg, 0.08 mmol) was dissolved in DMF (2 mL) along with *N*-Z-Gla-OH **19a** (28 mg, 0.076 mmol). To this solution was added, successively, a solution of DPPA (20 μL, 0.093 mmol) in DMF (0.5 mL) and Et_3N (13 μL, 0.093 mmol) at 0 °C under N_2. The solution was stirred for 22 h at the same temperature and was then diluted with ethyl acetate. The mixture was washed, successively, with 1 N aqueous HCl, brine, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica

gel (methanol/chloroform, 1/49, then 1/24) to give **26a** (40 mg, 55%) as an amorphous solid: $[\alpha]^{25}_D$ +1.0° (*c* 0.93, $CHCl_3$); IR (neat) 3336, 2984, 2940, 1676, 1520, 1482, 1456, 1422, 1394, 1370, 1278, 1248, 1170, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35, 1.43, 1.44, 1.45 (each s, 33 H), 1.10–1.88 (m, 8 H), 2.08 (s, 1 H), 2.24 (m, 2 H), 2.87 (s, 3 H), 2.94–3.40 (m, 8 H), 3.40–4.56 (m, 11 H), 5.08 (s, 2 H), 5.64 (br d, 1 H, *J* = 10 Hz), 6.94 (br s, 1 H), 7.34 (s, 5 H), 7.62 (br s, 1 H), 7.90 (br s, 1 H); MS (SIMS) *m/z* 958 (M + Li)$^+$, 852; HRMS (FAB) *m/z* calcd for $C_{46}H_{78}O_{14}N_7$ (M + H)$^+$ 952.5606, found 952.5605.

3-*epi*-*N*-(Benzyloxycarbonyl)-5,7-isopropylidenegalantinyl-N^{β}-(*tert*-butoxycarbonyl)-N^{β}-methyl-L-α,β-diaminopropionylglycyl-N^5,N^8-bis-(*tert*-butoxycarbonyl)spermidine [3*R*-Z-Gla-N^{β}-Me-L-A_2Pr(Boc)-Gly-N^5,N^8-di-Boc-Spe(4,3)] (26b). The title compound (10 mg, 39%) was obtained by the coupling of **25** (20 mg, 0.027 mmol) with 3*R*-Gla **19b** (12 mg, 0.03 mmol) according to a procedure similar to that of **26a**. **26b**: amorphous solid; $[\alpha]^{25}_D$ −3.5° (*c* 1.10, $CHCl_3$); IR (neat) 3328, 2984, 2940, 1686, 1528, 1484, 1456, 1422, 1394, 1368, 1302, 1276, 1252, 1170, 1086, 754, 698, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.38 (s, 3 H), 1.43 (s, 9 H), 1.45 (s, 9 H), 1.46 (s, 9 H), 1.48 (s, 3 H), 1.12–2.00 (m, 8 H), 2.34 (m, 2 H), 2.88 (s, 3 H), 2.96–3.40 (m, 8 H), 3.44–4.60 (m, 11 H), 5.09 (s, 2 H), 5.70 (br d, 1 H, *J* = 10 Hz), 6.76 (br s, 1 H), 7.35 (s, 5 H), 7.40 (br s, 1 H), 7.90 (br s, 1 H); MS (SIMS) *m/z* 958 (M + Li)$^+$, 852, 652; HRMS (FAB) *m/z* calcd for $C_{46}H_{78}O_{14}N_7$ (M + H)$^+$ 952.5606, found 952.5612.

Galantin I (Orn) (5a). A solution of **26a** (14 mg, 0.015 mmol) in methanol (0.5 mL) was stirred over 10% palladium on carbon (1 mg) under H_2 (1 atm) for 14 h at room temperature. The solution was filtered and concentrated in vacuo to give an oily residue. The residue was purified by column chromatography on silica gel (methanol/chloroform, 1/19, then 1/4) to give pure amine **27a** (8.5 mg, 71%). This was dissolved in DMF (1 mL) along with **24b** [prepared by the hydrolysis of **24a** (18 mg, 0.018 mmol); 1 N NaOH, THF, 0 °C, 14 h; 100%] at 0 °C under N_2. To this solution was added a solution of DPPA (5 μL, 0.023 mmol) in DMF (0.1 mL) and powdered $NaHCO_3$ (7.5 mg, 0.089 mmol). The reaction was vigorously stirred for 30 h at 0 °C. The solution was diluted with ethyl acetate and washed with 1 N aqueous HCl, brine, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (methanol/chloroform, 1/49, then 1/19) and preparative TLC (methanol/chloroform, 1/9) to give **28a** (11 mg, 59%). A solution of **28a** (4 mg, 0.002 mmol) in methylene chloride (0.5 mL) was treated with TFA (0.5 mL) for 2.5 h at room temperature. The solution was concentrated in vacuo, and the residue was purified by HPLC (CH_3CN/0.1% aqueous TFA, 1/99)[7] to give galantin I (Orn) (**5a**) (3 mg, 76%) as an amorphous solid: CD (*c* 0.036, H_2O); λ_{max} 199.6 (Δε −4.3), λ 200 (Δε −4.2), λ 220 (Δε −2.2); ^1H NMR (500 MHz, D_2O) δ 1.46 (d, 3 H, *J* = 7.5 Hz; D-Ala-CH_3), 1.43–1.98 (m, 18 H), 2.07 (m, 2 H, Spe N-CH_2-CH_2-CH_2-N), 2.49 (dd, 1 H, *J* = 10, 15 Hz, Gla 2-H), 2.59 (dd, 1 H, *J* = 3.5, 15 Hz, Gla 2-H), 2.78 (s, 3 H, N-CH_3), 3.01 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.02 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.08 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.09 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.14 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.23 (t, 2 H, *J* = 7 Hz, N-CH_2), 3.31 (dd, 1 H, *J* = 8, 13 Hz, L-A_2Pr 3-H), 3.35 (dd, 1 H, *J* = 8, 13 Hz, N^{β}-Me-L-A_2Pr 3-H), 3.36 (ddd, 1 H, *J* = 4, 5, 11 Hz, Glm 6-H), 3.54 (dd, 1 H, *J* = 5.5, 13 Hz, L-A_2Pr 3-H), 3.57 (dd, 1 H, *J* = 5.5, 13 Hz, N^{β}-Me-L-A_2Pr 3-H), 3.62 (dd, 1 H, *J* = 7.5, 11.5 Hz, Gla 7-H), 3.73 (dd, 1 H, *J* = 5.5, 11.5 Hz, Gla 7-H), 3.89 (m, 1 H, Gla 6-H), 3.90 (d, 1 H, *J* = 18 Hz, Gly), 3.93 (d, 1 H, *J* = 18 Hz, Gly), 4.02 (m, 1 H, Gla 5-H), 4.11 (ddd, 1 H, *J* = 2, 2, 11 Hz, Glm 5-H), 4.14 (d, 1 H, *J* = 2 Hz, Glm 2-H), 4.20 (ddd, 1 H, *J* = 2, 2, 10.5 Hz, Glm 3-H), 4.26 (m, 1 H, Gla 3-H), 4.39 (dd, 1 H, *J* = 6, 9 Hz, D-Orn 2-H), 4.43 (q, 1 H, *J* = 7.5 Hz, D-Ala 2-H), 4.88 (dd, 1 H, *J* = 5.5, 8 Hz, N^{β}-Me-L-A_2Pr 2-H), almost all of the protons were assigned using H,H-COSY; MS (SIMS) 981 (M + H)$^+$, 491; HRMS (FAB) *m/z* calcd for $C_{41}H_{85}O_{13}N_{14}$ (M + H)$^+$ 981.6421, found 981.6440.

3-*epi*-Galantin I (Orn) (5b). By the same procedure as that described in the preparation of **5a**, the protected form of **5b**, **28b**, (17 mg, 70%) was obtained by the coupling of **26b** (22 mg, 0.022 mmol) with **24b** (18 mg, 0.019 mmol). A solution of **28b** (4.5 mg, 0.0025 mmol) was treated with TFA. The resulting solution was concentrated in vacuo and purified by HPLC[7] to give **5b** (3 mg, 67%) as an amorphous solid: CD (*c* 0.045, H_2O); λ_{max} 199.2 (Δε −3.8), λ 200 (Δε −3.7), λ 220 (Δε −1.6); ^1H NMR (500 MHz, D_2O) δ 1.46 (d, 3 H, *J* = 7 Hz, D-Ala CH_3), 1.4–2.0 (m, 18 H), 2.09 (m, 2 H, Spe N-CH_2-CH_2-CH_2-N), 2.46 (dd, 1 H, *J* = 10, 15 Hz, 3*R*-Gla 2-H), 2.64 (dd, 1 H, *J* = 3, 15 Hz, 3*R*-Gla 2-H), 2.80 (s, 3 H, N-CH_3), 3.03 (t, 2 H, *J* = 7 Hz, N-CH_2), 3.03 (t, 2 H, *J* = 7 Hz, N-CH_2), 3.09 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.10 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.15 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.24 (t, 2 H, *J* = 7 Hz, N-CH_2), 3.32 (dd, 1 H, *J* = 8, 13 Hz, L-A_2Pr 3-H), 3.34–3.40 (m, 2 H, N^{β}-Me-L-A_2Pr 3-H and Glm 6-H), 3.55 (dd, 1 H, *J* = 6, 13 Hz, L-A_2Pr 3-H), 3.58 (dd, 1 H, *J* = 5.5, 13 Hz, N^{β}-Me-L-A_2Pr 3-H), 3.63 (dd, 1 H, *J* = 7.5, 11.5 Hz, 3*R*-Gla 7-H), 3.74 (dd, 1 H, *J* = 5, 11.5 Hz, 3*R*-Gla 7-H), 3.90 (d, 1 H, *J* = 18 Hz, Gly), 3.94 (d, 1 H, *J* = 18 Hz, Gly), 3.95–4.01 (m, 2 H, 3*R*-Gla 5-H and 6-H), 4.12 (ddd, 1 H, *J* = 2, 2, 10.5 Hz, Glm 5-H), 4.15 (d, 1 H, *J* = 2 Hz, Glm 2-H), 4.21 (ddd, 1 H, *J* = 2, 2, 10.5 Hz, Glm 3-H), 4.27 (m, 1 H, 3*R*-Gla 3-H), 4.39 (dd, 1 H, *J* = 6, 9 Hz, D-Orn 2-H), 4.44 (q, 1 H, *J* = 7.5 Hz, D-Ala 2-H), 4.88 (dd, 1 H, *J* = 5.5, 8 Hz, N^{β}-Me-L-A_2Pr 2-H), almost all of the protons were assigned using H,H-COSY; MS (SIMS) 981 (M + H)$^+$, 491; HRMS (FAB) *m/z* calcd for $C_{41}H_{85}O_{13}N_{14}$ (M + H)$^+$ 981.6421, found 981.6430.

Galantin I (Lys) (5c). The protected galantin I (Lys) (**29**) (7 mg, 45%) was obtained by the coupling of **24c** (18 mg, 0.017 mmol) with **26a** (12 mg, 0.013 mmol) as described in the preparation of **5a**. A solution of **29** (3 mg, 0.0017 mmol) in methylene chloride (0.5 mL) and TFA (0.5 mL) was stirred for 2.5 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by HPLC[7] to give **5c** (2 mg, 67%) as an amorphous solid: CD (*c* 0.055, H_2O); λ_{max} 198.6 (Δε −3.1), λ 200 (Δε −2.9), λ 220 (Δε −1.2); ^1H NMR (500 MHz, D_2O) δ 1.47 (d, 3 H, *J* = 7.5 Hz, D-Ala CH_3), 1.40–1.95 (m, 20 H), 2.09 (m, 2 H, Spe N-CH_2-CH_2-CH_2-N), 2.50 (dd, 1 H, *J* = 10, 15 Hz, Gla 2-H), 2.60 (dd, 1 H, *J* = 3.5, 15 Hz, Gla 2-H), 2.80 (s, 3 H, N-CH_3), 3.00 (t, 2 H, *J* = 7.5 Hz, N-CH_2), 3.04 (t, 2 H, *J* = 7.5 Hz, N-CH_2), 3.10 (t, 2 H, *J* = 7.5 Hz, N-CH_2), 3.11 (t, 2 H, *J* = 7.5 Hz, N-CH_2), 3.16 (t, 2 H, *J* = 8 Hz, N-CH_2), 3.25 (t, 2 H, *J* = 7 Hz, N-CH_2), 3.32 (dd, 1 H, *J* = 8, 13.5 Hz, L-A_2Pr 3-H), 3.36 (dd, 1 H, *J* = 8, 13 Hz, N^{β}-Me-L-A_2Pr 3-H), 3.39 (m, 1 H, Glm 6-H), 3.54 (dd, 1 H, *J* = 5, 13.5 Hz, L-A_2Pr 3-H), 3.59 (dd, 1 H, *J* = 5.5, 13 Hz, N^{β}-Me-L-A_2Pr 3-H), 3.63 (dd, 1 H, *J* = 7, 11.5 Hz, Gla 7-H), 3.74 (dd, 1 H, *J* = 5, 11.5 Hz, Gla 7-H), 3.91 (m, 1 H, Gla 6-H), 3.92 (d, 1 H, *J* = 17 Hz, Gly), 3.95 (d, 1 H, *J* = 17 Hz, Gly), 4.04 (m, 1 H, Gla 5-H), 4.13 (ddd, 1 H, *J* = 2, 2.5, 11 Hz, Glm 5-H), 4.15 (d, 1 H, *J* = 2 Hz, Glm 2-H), 4.22 (ddd, 1 H, *J* = 2, 2, 10.5 Hz, Glm 3-H), 4.28 (m, 1 H, Gla 3-H), 4.37 (dd, 1 H, *J* = 5, 8 Hz, D-Lys 2-H), 4.45 (g, 1 H, *J* = 7.5 Hz, D-Ala 2-H), almost all of the protons were assigned using H,H-COSY; MS (SIMS) 995 (M + H)$^+$, 498; HRMS (FAB) *m/z* calcd for $C_{42}H_{87}O_{13}N_{14}$ (M + H)$^+$ 995.6578, found 995.6581.

(4*R*)-3-(*N*-*tert*-Butoxycarbonyl)-4-(3-hydroxy-1(*Z*)-propen-1-yl)-2,2-dimethyl-1,3-oxazolidine (34). To a suspension of NaH (210 mg, 5.25 mmol) in THF (12 mL) at 0 °C under N_2 was added a solution of bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate (1.10 mL, 4.02 mmol) in THF (6 mL), drop by drop, over 5 min. The suspension was stirred for 30 min at 0 °C and then cooled to −78 °C. To this mixture were added, successively, a solution of 18-crown-6 (6.9 g, 26.1 mmol) in THF (26 mL) and a solution of **30** (0.92 g, 4.02 mmol) in THF (10 mL). After being stirred for 1.5 h at −78 °C, the mixture was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1/3) to give a mixture of **33** and its *E* isomer (1.17 g, 82%; **33**/*E* isomer = 9/1). To a solution of this mixture (1.17 g, 4.10 mmol) in methylene chloride (20 mL) was added BF_3·OEt_2 (505 μL, 4.10 mmol) at −78 °C under N_2. The solution was stirred for 30 min at −78 °C, and to this was added a solution of diisobutylaluminum hydride (DIBAL; 1 M solution in hexane; 10 mL, 10 mmol). The solution was stirred for 1.5 h at −78 °C and quenched with methanol. The solution was allowed to warm to 0 °C. To this mixture was added 10% aqueous tartaric acid (40 mL). The mixture was extracted with methylene chloride, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to give an oily residue. This, upon purification by column chromatography on silica gel (Et_2O/hexane, 3/7, 1/1, then 3/2), gave **34** (0.62 g, 60% from **30**) as an oil: $[\alpha]^{25}_D$ +28.6° (*c* 1.38, $CHCl_3$); IR ($CHCl_3$) 3444, 3012, 2892, 2884, 1676, 1400, 1392, 1370, 1108, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.45 (s, 9 H), 1.48 (s, 3 H), 1.57 (s, 3 H), 3.69 (dd, 1 H, *J* = 1.5, 9 Hz), 3.88 (m, 1 H), 4.04 (dd, 1 H, *J* = 6, 9 Hz), 4.14 (br s, 0.5 H), 4.23 (br s, 0.5 H), 4.42 (br dd, 1 H, *J* = 8.5, 12 Hz), 4.90 (br dd, 1 H, *J* = 6.5, 10 Hz), 5.53 (t, 1 H, *J* = 10.5 Hz), 5.85 (ddd, 1 H, *J* = 6.5, 8.5, 10.5 Hz); MS (SIMS) *m/z* 258 (M + H)$^+$. Anal. Calcd for $C_{13}H_{23}O_4N$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.92; H, 9.29; N, 5.54.

(4*S*,1′*R*,2′*S*)-3-(*N*-*tert*-Butoxycarbonyl)-4-(3-hydroxy-1,2-epoxypropan-1-yl)-2,2-dimethyl-1,3-oxazolidine (35). To a solution of **34** (620 mg, 2.41 mmol) in methylene chloride (20 mL) was added MCPBA (625 mg, 2.90 mmol) at 0 °C. After being stirred for 15 h at the same temperature, the mixture was quenched with 5% aqueous K_2CO_3 and extracted with chloroform. The extract was dried ($MgSO_4$) and concentrated in vacuo to give a crude residue. This, upon purification by column chromatography on silica gel (Et_2O/hexane, 3/7, then 1/1), gave **35** (615 mg, 93%) as colorless crystals: mp 78.5–79.0 °C; $[\alpha]^{25}_D$ +12.2° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3460, 2992, 2944, 2892, 1692, 1394, 1370,

1256, 1104, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.50 (s, 12 H), 1.64 (br s, 3 H), 1.67 (s, 1 H), 3.14 (m, 2 H), 3.86 (br d, 1 H, J = 8.5 Hz), 3.87 (m, 2.5 H), 4.03 (dd, 1 H, J = 6.5, 9.5 Hz), 4.20 (br s, 0.5 H); MS (SIMS) m/z 274 $(M + H)^+$. Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.12; H, 8.48; N, 5.13. Found: C, 57.00; H, 8.62; N, 5.10.

(6*S*,4'*S*)-5,6-Dihydro-6-[*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl)-2-pyrone (39). To a solution of oxalyl chloride (1.56 mL, 17.87 mmol) in methylene chloride (10 mL) at −78 °C under N_2 was added a solution of dimethyl sulfoxide (DMSO) (1.59 mL, 22.41 mmol) in methylene chloride (10 mL), drop by drop, over 5 min. After the solution was stirred for 10 min, to it at −90 °C was added a solution of **35** (2.30 g, 8.94 mmol) in methylene chloride (30 mL), drop by drop, over 15 min. The reaction mixture was stirred for 15 min at −90 °C. To the resulting solution was added Et_3N (10 mL, 71.7 mmol), drop by drop, over 5 min. The mixture was stirred for an additional 10 min and quenched with saturated aqueous NH_4Cl. The mixture was extracted with chloroform and Et_2O several times. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a crude residue which, upon purification by column chromatography on silica gel (Et_2O/hexane, 3/7, then 1/1), gave an aldehyde (2.00 g, 87%). The aldehyde (2.00 g, 7.38 mmol) was dissolved in benzene (10 mL) along with methyl (triphenylphosphoranylidene) acetate (3.70 g, 11.07 mmol). The mixture was stirred for 14 h at room temperature under N_2. The solution was concentrated in vacuo to give an oily residue which, upon purification by column chromatography on silica gel (Et_2O/hexane, 1/9), gave a mixture of Z and E α,β-unsaturated epoxy esters **37** (2.22 g, 92%; Z/E = 1/2). To a solution of diphenyl diselenide (3.7 g, 11.9 mmol) in ethanol (30 mL) was added sodium borohydride ($NaBH_4$) (900 mg, 23.8 mmol) at room temperature. After being stirred for a few minutes, the resulting clear yellow solution was added to a solution of **37** (2.55 g, 7.90 mmol) in ethanol (10 mL). The reaction mixture was stirred for 2 h at room temperature. Oxygen gas was then passed through this mixture.[27] The mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O/hexane, 1/1, then Et_2O) to give β,γ-unsaturated ester **38** (2.50 g, 97%; ~20% of its corresponding ethyl ester was contaminated and was inseparable from **38**). This ester (1.07 g, 3.22 mmol) was dissolved in benzene (7 mL) along with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (24 μL, 0.16 mmol). The solution was refluxed for 48 h under N_2. Then the solution was concentrated in vacuo. The residue was purified, successively, by column chromatography on silica gel (ethyl acetate/benzene, 1/9, then 3/7) and by MPLC (ethyl acetate/benzene, 1/19) to give a mixture of inseparable **38** and **40a** (351 mg, 33%) and a mixture of inseparable **39** and the ethyl ester of **40a** (670 mg). The desired α,β-unsaturated δ-lactone **39** was isolated from the latter mixture (670 mg) by treatment with CSA (5 mg) in methylene chloride (8 mL) for 17 h at room temperature. The mixture was quenched with $NaHCO_3$ powder and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 3/7) to give **39** (438 mg, 46%) as colorless crystals: mp 88–88.5 °C; $[\alpha]^{25}_D$ −68.4° (c 1.05, $CHCl_3$); IR ($CHCl_3$) 2992, 1732, 1700, 1380, 1370, 1256, 1098, 1068, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.47 (s, 3 H), 1.49 (s, 9 H), 1.57, 1.62 (pair of s, 3 H), 2.31 (m, 1 H), 2.49 (m, 1 H), 4.02 (dd, 1 H, J = 6.5, 10 Hz), 4.16 (br d, 1 H, J = 10 Hz), 4.17, 4.29 (pair of m, 1 H), 4.78, 4.95 (pair of m, 1 H), 6.03 (m, 1 H), 6.93 (m, 1 H); MS (SIMS) m/z 298 $(M + H)^+$. Anal. Calcd for $C_{15}H_{23}O_5N$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.67; H, 7.93; N, 4.72. The mixture of **38** and **40a** was recycled by the treatment with DBU to give **39** as described above.

(2*R*,3*R*,5*S*,4'*S*)-5-[3-*N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]-2,3-epoxy-5-pentanolide (41). To a solution of **39** (200 mg, 0.67 mmol) in THF (2 mL) at 0 °C were added 40% aqueous benzyltrimethylammonium hydroxide (Triton B) (26 μL, 0.07 mmol) and *tert*-butyl hydroperoxide (138 μL, 1.01 mmol). The solution was stirred for 20 min, diluted with water, and quenched with 1 N HCl. The solution was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue. This, upon successive purification by column chromatography on silica gel (Et_2O, then ethyl acetate/benzene, 1/19) and by MPLC (ethyl acetate/benzene, 1/19), gave **41** (96 mg, 42%) and starting lactone **39** (107 mg). **41**: colorless solid, mp 103.5–104 °C; $[\alpha]^{25}_D$ +19.1° (c 1.01, $CHCl_3$); IR ($CHCl_3$) 2992, 2948, 2900, 1750, 1700, 1380, 1370, 1268, 1090, 1066, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.48 (br s, 12 H), 1.57, 1.62 (pair of s, 3 H), 2.07 (dd, 1 H, J = 12.5, 15 Hz), 2.38 (ddd, 1 H, J = 2.5, 2.5, 15 Hz), 3.58 (m, 1 H), 3.72 (m, 1 H), 3.96 (m, 2 H), 4.10, 4.24 (pair of br s, 1 H), 4.87, 4.97 (pair of m, 1 H); MS (SIMS) m/z 314 $(M + H)^+$. Anal. Calcd for $C_{15}H_{23}O_6N$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.21; H, 7.54; N, 4.46.

(3*R*,5*S*,4'*S*)-5-[3-*N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]-3-hydroxy-5-pentanolide (42a). To a solution of diphenyl diselenide (151 mg, 0.48 mmol) in 2-propanol (2 mL) at room temperature was added $NaBH_4$ (37 mg, 0.98 mmol). After this solution was stirred for 5 min, to it was added acetic acid (55 μL, 0.96 mmol). After it was stirred for an additional 5 min, the resulting yellow suspension was added to a solution of epoxy lactone **41** (101 mg, 0.32 mmol) in 2-propanol (2 mL). The solution was stirred for 15 min at room temperature. The mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude residue. This, upon purification by column chromatography on silica gel (Et_2O, then ethyl acetate), gave **42a** (96 mg, 94%) as colorless crystals: mp 119–120 °C; $[\alpha]^{25}_D$ −19.4° (c 0.97, $CHCl_3$); IR ($CHCl_3$) 3620, 3476, 3040, 2992, 2944, 1740, 1696, 1382, 1370, 1256, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.50 (s, 9 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.83 (m, 1 H), 1.97 (m, 1 H), 2.68 (m, 1 H), 2.72 (dd, 1 H, J = 4.5, 13 Hz), 4.00 (m, 2 H), 4.20, 4.31 (pair of m, 1 H), 4.44 (m, 1 H), 5.15 (m, 1 H); MS (SIMS) m/z 316 $(M + H)^+$. Anal. Calcd for $C_{15}H_{25}O_6N$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.89; H, 8.14; N, 4.58.

(3*S*,5*S*,4'*S*)-5-[3-*N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]-3-[(*tert*-butyldimethylsilyl)oxy]-5-pentanolide (45b). To a solution of DMSO (15.5 μL, 0.22 mmol) in methylene chloride (100 μL) at −78 °C was added a solution of trifluoroacetic anhydride (TFAA) (23 μL, 0.16 mmol) in methylene chloride (100 μL) under N_2. After this solution was stirred for 15 min, to it at −78 °C was added a solution of **42a** (31 mg, 0.10 mmol) in methylene chloride (250 μL), drop by drop, over 10 min. The solution was stirred for 15 min at the same temperature. To this solution was added Et_3N (45 μL, 0.3 mmol), drop by drop, over 30 min. After being stirred for an additional 15 min at the same temperature, the reaction was quenched with 2-propanol and saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo to give crude **44**, which was dissolved in THF (500 μL) and water (50 μL) along with NH_3·BH_3 (3.4 mg, 0.11 mmol). To this solution was added 1 M aqueous citric acid (110 μL, 0.11 mmol), drop by drop, over 30 min. After being stirred for 30 min, the mixture was diluted with ethyl acetate and washed, successively, with 1 N HCl, water, saturated aqueous $NaHCO_3$, and water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oily residue which, upon purification by silica gel column chromatography (Et_2O, then ethyl acetate), gave an inseparable mixture of **42a** and **45a** (24 mg, 77%; **42a**/**45a** = 1/3). This was separated by conversion to a mixture of the corresponding TBS ethers, **42b** and **45b**, as follows. To a solution of this mixture (51 mg, 0.16 mmol) in methylene chloride (500 μL) were added, successively, 2,6-lutidine (29 μL, 0.25 mmol) and TBSOTf (56 μL, 0.24 mmol) at −78 °C under N_2. The solution was stirred for 10 min at the same temperature and was then quenched with saturated aqueous NH_4Cl. The solution was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue, upon purification by column chromatography on silica gel (Et_2O/hexane, 3/7, then Et_2O) and by preparative TLC (Et_2O/hexane, 3/1), gave **45b** (35 mg, 50%), **42b** (5 mg, 7%), and α,β-unsaturated δ-lactone **39** (6 mg, 12%; dehydrated under the reaction conditions), respectively. **45b**: colorless crystals, mp 107.5–108 °C; $[\alpha]^{25}_D$ −32.2° (c 1.53, $CHCl_3$); IR ($CHCl_3$) 2964, 2940, 2896, 2864, 1740, 1698, 1380, 1370, 1258, 1092, 1060, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.47 (br s, 3 H), 1.49 (br s, 9 H), 1.57, 1.62 (pair of s, 3 H), 1.70 (m, 1 H), 2.08 (m, 1 H), 2.46 (dd, 1 H, J = 7, 12 Hz), 2.81 (m, 1 H), 3.98 (dd, 1 H, J = 6.5, 10 Hz), 4.02 (m, 1 H), 4.16 (m, 1.5 H), 4.28 (m, 0.5 H), 4.54, 4.75 (pair of m, 1 H); MS (SIMS) m/z 430 $(M + H)^+$, 316. Anal. Calcd for $C_{21}H_{39}O_6NSi$: C, 58.71; H, 9.15; N, 3.26. Found: C, 58.45; H, 9.30; N, 3.20.

Galantinic Acid (20a). A solution of **45b** (37 mg, 0.09 mmol) in methylene chloride (0.5 mL) and TFA (0.5 mL) was stirred for 15 min at room temperature. The reaction mixture was concentrated in vacuo to give an oily residue. The residue was passed through a column of Dowex 50Wx4 (100–200 mesh) ion exchange resin (H_2O, then 1 N aqueous NH_3) to give **20a** as crude crystals. These were recrystallized from H_2O/MeOH to give pure **20a** (16 mg, 96%): colorless crystals, mp 125–130 °C dec; $[\alpha]^{25}_D$ −29.4° (c 0.5, H_2O); IR (KBr) 3339.6, 1651.8, 1615.2, 1562.1 cm^{-1}; ^1H NMR (360 MHz, D_2O) δ 1.67 (m, 2 H), 2.38 (dd, 1 H, J = 6, 14 Hz), 2.45 (dd, 1 H, J = 7.5, 14 Hz), 3.18 (ddd, 1 H, J = 4, 7, 7 Hz), 3.69 (dd, 1 H, J = 7, 12 Hz), 3.84 (dd, 1 H, J = 4, 12 Hz), 3.94 (ddd, 1 H, J = 6, 6, 7 Hz), 4.21 (dddd, 1 H, J = 6, 6, 7.5, 7.5 Hz); MS (SIMS) 194 $(M + H)^+$; HRMS (FAB) m/z calcd for $C_7H_{16}O_5N$ $(M + H)^+$ 194.1028, found 194.1030.

3-*epi*-Galantinic Acid (20b). The title compound (5.5 mg, 82%) was obtained from **42a** (11 mg, 0.035 mmol) by the same treatment as described above. **20b**: colorless crystals, mp 186.0–188.0 °C; $[\alpha]^{25}_D$ −5.8° (c 0.5, H_2O); IR (KBr) 3372.3, 1651.8, 1615.2, 1557.4 cm^{-1}; ^1H NMR (360 MHz, D_2O) δ 1.75 (ddd, 1 H, J = 8, 8, 14.5 Hz), 1.82 (ddd, 1 H, J = 5, 5.5, 14.5 Hz), 2.38 (dd, 1 H, J = 8, 15 Hz), 2.46 (dd, 1 H, J = 6, 15 Hz), 3.28 (ddd, 1 H, J = 4, 6, 7 Hz), 3.72 (dd, 1 H, J = 7, 12.5

Hz), 3.86 (dd, 1 H, J = 4, 12.5 Hz), 3.96 (ddd, 1 H, J = 5, 6, 8 Hz), 4.21 (dddd, 1 H, J = 5.5, 5.5, 8, 8 Hz); MS (SIMS) 194 $(M + H)^+$; HRMS (FAB) m/z calcd for $C_7H_{16}O_5N$ $(M + H)^+$ 194.1028, found 194.1029.

General Procedure for the Acid-Catalyzed Cyclization of Galantinic Acid and Its Analogues. Acid Treatment of Galantinic Acid. Galantinic acid (**20a**) (4 mg, 0.02 mmol) was dissolved in 6 N aqueous HCl and heated (110 °C) in a sealed tube. After 14 h, the solution was concentrated in vacuo. The residue was passed through a column of Dowex 50Wx4 (100-200 mesh) ion exchange resin (H_2O, then 1 N aqueous NH_3) to give a mixture of **3a** and **3b** (2.8 mg, 77%). The mixture was dissolved in 1 N HCl and concentrated in vacuo to give a mixture of **3a** and **3b** as hydrochlorides. Using these hydrochlorides, the product ratio (**3a**/**3b**) was calculated from the integration of the ^1H NMR (D_2O, 270 MHz) spectrum of the mixture of **3a** and **3b**: the signal of 3βH of **3a** appeared at δ 2.20 (ddd, 1 H, J = 2.4, 5.3, 12.5 Hz) and that of 3αH and 3βH of **3b** appeared at δ 1.85 (m, 2 H).[4] The ratio of **3a**/**3b** was 9/1.

Acid Treatment of 3-*epi*-Galantinic Acid (20b). According to the general procedure, **20b** (5.5 mg, 0.03 mmol) gave a mixture of **3a** and **3b** (2.1 mg, 42%). The ratio of **3a**/**3b** was 11/1.

Acid Treatment of 3a. According to the general procedure, **3a** (4 mg, 0.02 mmol) gave a mixture of **3a** and **3b** (4 mg, 100%). The ratio of **3a**/**3b** was 8/1.

Acid Treatment of 3b. *N*-(*tert*-Butoxycarbonyl)-**3b** (5 mg, 0.02 mmol) was exposed to 6 N aqueous HCl for 14 h at 110 °C in a sealed tube. The solution was concentrated in vacuo. The residue was dissolved in dioxane (0.5 mL) and H_2O (0.5 mL). The solution was adjusted to pH 8 by adding Et_3N. To this solution was added Boc_2O (10 μL, 0.04 mmol). The solution was stirred for 3 h at room temperature and then adjusted to pH 2 with 1 N aqueous HCl. The resulting solution was extracted with ethyl acetate several times, and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. To a solution of the residue in Et_2O was added diazomethane in Et_2O. The solution was concentrated in vacuo to give an oily residue, which was chromatographed on silica gel to give a mixture of **3a'** and **3b'** (2 mg, 38%; **3a'**/**3b'** = 2/7 by ^1H NMR analysis).

Acid Treatment of *E* Unsaturated Acid 46. Protected *E* α,β-unsaturated acid **46** (17 mg, 0.06 mmol), which was prepared from **40a** by hydrolysis (0.5 N NaOH, room temperature, 4 h), was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (8.4 mg, 88%). The ratio of **3a**/**3b** was 2/1.

Acid Treatment of *Z* Unsaturated Acid 47. α,β-Unsaturated δ-lactone **39** (17 mg, 0.06 mmol) was hydrolyzed with 0.5 N aqueous NaOH (140 μL) for 4 h at 0 °C in THF (280 μL). The solution was adjusted to pH 2 with 1 N aqueous HCl, extracted with ethyl acetate, and washed with water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the N-protected form of the *Z* unsaturated acid **47**. This was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (8.4 mg, 85%). The ratio of **3a**/**3b** was 9/1.

Acid Treatment of α,β-Unsaturated Lactone 48. α,β-Unsaturated δ-lactone **39** (10 mg, 0.03 mmol), which was used as an equivalent compound of **48**, was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (4.7 mg, 80%). The ratio of **3a**/**3b** was 10/1.

Acid Treatment of 3(*S*)-Hydroxy δ-Lactone 49. A solution of **45b** (10 mg, 0.02 mmol) in methylene chloride (100 μL) and TFA (100 μL) was stirred for 20 min at room temperature. The solution was concentrated in vacuo to give **49** as the corresponding TFA salt. This was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (4 mg, 98%). The ratio of **3a**/**3b** was 11/1.

Acid Treatment of 3(*R*)-Hydroxy δ-Lactone 50. 3(*R*)-Hydroxy lactone **42a** (10 mg, 0.03 mmol), which was used as an equivalent compound of **50**, was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (5.5 mg, 99%). The ratio of **3a**/**3b** was 11/1.

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Supplementary Material Available: Detailed description of syntheses and spectral data of compounds **1a**, **4a**, and **4b** and ^1H NMR spectra of **1a**, **4a**, **4b**, **5c**, **20a**, **20b**, and other key synthetic intermediates (12 pages). Ordering information is given on any current masthead page.

Regiospecific Synthesis of Polysubstituted Naphthalenes via Oxazoline-Mediated Nucleophilic Aromatic Substitutions and Additions

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Abstract: An efficient procedure for the selective functionalization of several positions of 2-methoxynaphthalene is described. Nucleophilic aromatic substitutions were carried out by displacing both a methoxy group and a neutral amine ortho to an oxazoline **6**. 4-Substituted naphthalenes **8** were obtained from nucleophilic aromatic addition of an allyllithium species to a position para to the oxazoline **6**. The resultant dihydronaphthalenes were converted to the fully aromatic systems **9** or alternatively substituted in the 2-position to form **10**. Reductive cleavage of the oxazoline moities in **7** and **9** proceeded smoothly, producing the substituted naphthaldehydes **11**.

The functionalization of naphthalenes has become a prominent route by which many important organic compounds are accessed. In view of a recent report[1] describing substitution in the naphthalene series via aryne intermediates wherein a single substituent is introduced, we are prompted to disclose our own efficient effort in performing multiple selective substitutions.[2] The widespread use of naphthalenes as a starting material in synthesis stems from the ubiquitous nature of fused 6,6-ring systems in naturally-occurring compounds, including saturated as well as unsaturated variants. Unfortunately, substituted naphthalenes have often

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(2) For our previous contributions, see: (a) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178-7184 (aryne chemistry). (b) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607-2609 and references cited therein (naphthalene substitutions).

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