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EFFICIENT SYNTHESIS OF THE REVISED STRUCTURE OF (-)-GALANTINIC ACID.

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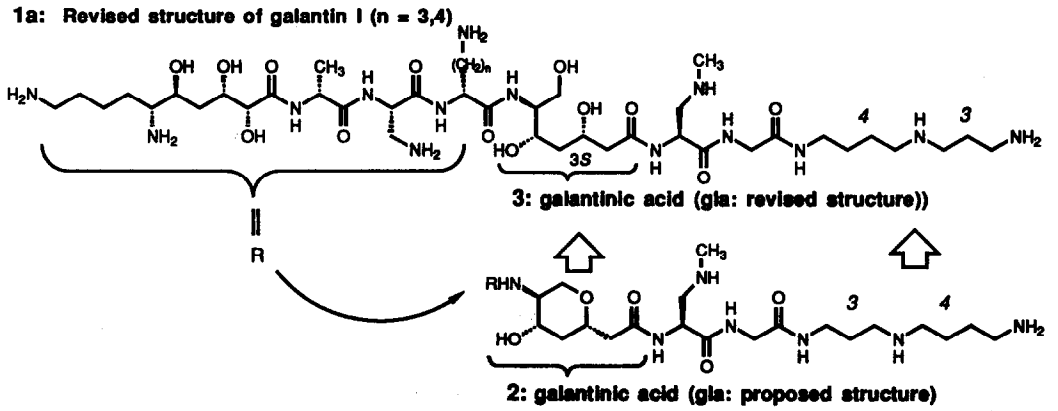
Summary: The synthesis of the revised structure of galantinic acid was accomplished starting from the serinal derivative **4** via a stereoselective epoxidation of hydroxymethyl-*Z*-allyl amine **5** and δ-substituted-α,β-unsaturated-δ-lactone **9**.

Galantinic acid (gla) was found as a constituent amino acid of the peptide antibiotic galantin I.[1] The structure of gla was originally assigned as **2** which was isolated from the mother peptide by chemical degradation, and has received much attention in view of asymmetric synthesis of 1,2-aminohydroxyl system involved in its structure.[2] However, the originally isolated gla **2** was an artifact and the structure of gla had to be revised to **3**. Both **3** and its diastereomer at C-3 were prepared in a masked form for the total synthesis of galantin I (**1a**) by us.[3] We report herein the synthesis of natural gla **3**.

The key step of the synthesis is characterized by the stereocontrolled introduction of the 3,5-dihydroxyl groups of **3** using an epoxidation strategy to both the acyclic and cyclic intermediates, **5** and **9**, respectively. Thus, the synthesis began with the readily available L-serinal derivative **4**,[4] which was converted into the *Z*-allyl alcohol **5** using standard procedures. Epoxidation of **5**



with MCPBA furnished the epoxy alcohol **6**, exclusively, with the desired (2*S*,3*R*) stereochemistry which was in accord with the epoxidation of related systems.[5] Elongation of the C2 unit to **6** was carried out by (1) Swern oxidation at -90 °C and (2) Ph_3PCHCO_2Me to give a mixture of ***Z*** and ***E*** unsaturated esters **7** (***E*/*Z*** = 2/1). The epoxide of **7** was cleaved reductively by the use of Miyashita's reagent[6] to give the β,γ-unsaturated ester **8** as a single regioisomer which upon treatment with DBU gave desired **9** accompanied by starting **8** and isomerized **10** (**8/9/10** = 1/4/4). Since treatment of **10** under the same conditions gave the same product mixture, **9** could be produced via the ***Z***-isomer of **10**. Recovered **8** and **10** were recycled and gave **9**. Introduction of the hydroxyl group at C-3 into **9** was accomplished by epoxidation of the lactone **9** with *t*-BuOOH in the presence of catalytic Triton B followed by reduction with modified Miyashita's conditions (3 equiv of PhSeH prepared from 3 equiv of $Na^+[PhSeB(Oi\text{-}Pr)_3]^-$ and 3 equiv of AcOH)[7] to give the (3*R*)-hydroxy lactone **12** as the sole product.[8] The exclusive formation of a single diastereomer under the epoxidation stage was attributed to an axial attack[9] of the reagent to the conformer **A** resulting in the formation of **12**. The configuration of the natural isomer at C-3 was *S*. Therefore, inversion of this stereochemistry was examined as follows. Although initially the oxidation of **12** was accompanied by difficulties such as low yields due to β-elimination of the hydroxyl group of **12** or overoxidation of the product, these were overcome by the use of TFAA/DMSO[10]. The product **13** was immediately reduced with $NH_3 \cdot BH_3$[11] to give a mixture of (3*S*)-**14** and **12** with moderate stereoselectivity (76% from **12**; **14/12** = 3/1 by ^1H NMR). These were separated chromatographically by converting them into the corresponding silyl ether **15** and its C-3 epimer. Finally, exposure of **15** to TFA followed by treatment with Dowex 50Wx4 (elution with 1 N NH_3) gave the desired **3** in quantitative yield. The epimer of gla at C-3 was obtained from **12** by the same treatment as above. Thus, the synthesis of gla was accomplished starting from **4**. This is the first report introducing physical as well as spectroscopic data of (-)-galantinic acid.[12] Further studies related to stereospecific cyclization of **3** to **2**, which occurred under the degradation conditions, will be reported in due course.

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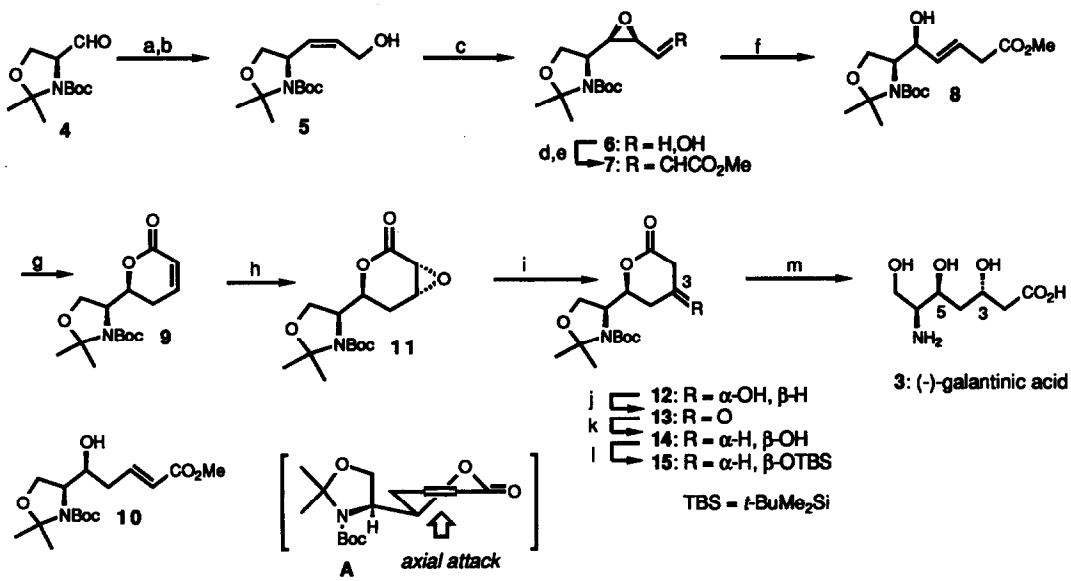

[a](a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6, THF, -78 °C, 2 h (82%); (b) *i*-Bu_2AlH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, -78 °C, 1.5 h (73%); (c) 3-chloroperbenzoic acid (MCPBA), CH_2Cl_2, 0 °C, 12 h (67%); (d) $(COCl)_2$, DMSO, CH_2Cl_2, -90 °C, 15 min, Et_3N, -90 °C, 10 min (87%); (e) Ph_3PCHCO_2Me, benzene, room temperature, 14 h (92%); (f) $Na^+[PhSeB(OEt)_3]^-$, EtOH, room temperature, 1 h (94%); (g) 0.05 equiv of 1,8-diazabicyclo[5,4.0]undec-7-ene (DBU), benzene, reflux, 60 h (**9**: 42%, **8**: 10%, and **10**: 42%); (h) *t*-BuOOH, 0.1 equiv of Triton B,THF, 0 °C, 15 min (**11**: 42% and **9**: 54%); (i) PhSeH, *i*-PrOH, room temperature, 15 min (94%); (j)1.5 equiv of trifluoroacetic anhydride (TFAA), DMSO, CH_2Cl_2, -78 °C,15 min, 3 equiv of Et_3N (dropwise addition over a period of 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 **12**; **14**/**12** =3/1), (k) *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, -78 °C, 15 min (64%); (m) trifluoroacetic acid (TFA), CH_2Cl_2, room temperature, 15 min; (2) Dowex 50Wx4 (elution with 1 N NH_3) (100%).

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4. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
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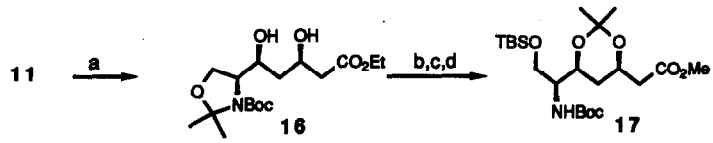
6. Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293. ~30% of the corresponding ethyl ester was contaminated in **8**.
7. Personal communication from Professor Masaaki Miyashita whom we gratefully acknowledge.

8. The configuration of the hydroxyl group of **11** were determined by converting it into the corresponding acetonide **17** of which the spectroscopic data were completely identical with those reported.



(a) 3 equiv of $Na^+[PhSeB(OEt)_3]^-$, 0.5 equiv of AcOH, EtOH, room temperature, 5 min (94%); (b) *dl*-10-camphorsulfonic acid (CSA), MeOH, room temperature, 48 h (52%); (c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 10 min (46%); (d) CSA, 2,2-dimethoxypropane, benzene, room temperature, 5 min (73%).

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12. Mp and $[\alpha]_D$ value of the key intermediates, **3** and 3'-epimer of **3** and ^1H NMR, IR, and MS data of **3** and 3'-epimer of **3**. **6**; mp 78.5-79.0 °C; $[\alpha]^{25}_D$ +12.2° (*c* 0.9, $CHCl_3$). **9**: mp 88.0-88.5 °C; $[\alpha]^{25}_D$ -68.4° (*c* 1.05, $CHCl_3$). **11**: mp 103.5-104.0 °C; $[\alpha]^{25}_D$ +19.1° (*c* 1.0, $CHCl_3$). **12**: mp 119.0-120.0 °C; $[\alpha]^{25}_D$ -19.4° (*c* 0.97, $CHCl_3$). **15**: mp 107.5-108.0 °C; $[\alpha]^{25}_D$ -32.2° (*c* 1.5, $CHCl_3$). Galantinic acid **3**: mp 125-130 °C (decomp); $[\alpha]^{25}_D$ -29.4° (*c* 0.5, H_2O); IR (KBr) 3339.6, 1651.8, 1615.2, 1562.1 cm^{-1}; MS (SIMS) 194 $(M+H)^+$; ^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). 3'-Epimer of **3**: 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}; MS (SIMS) 194 $(M+H)^+$; ^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). *TSP was used as the external standard.

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