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Stereoselective Synthesis of *N*-Boc-Galantinic Acid Ethyl Ester

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Abstract : An efficient synthesis of the biologically important title amino acid is described. The key features of the synthesis are, i) a chelation controlled Grignard reaction towards stereoselective formation of the *syn*-1,2-amino alcohol unit, and ii) construction of the *anti*-1,3-diol moiety *via* hydroxy group directed stereoselective reduction of a proximal ketone. © 1999 Elsevier Science Ltd. All rights reserved.

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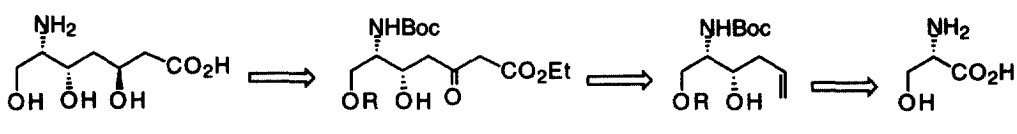
Galantinic acid (**1**), a constituent amino acid of the peptide antibiotic galantin I, was isolated from a culture broth of *Bacillus pulvifaciens* .[1] The originally assigned tetrahydropyranoid structure of galantinic acid was later revised to its acyclic form **1** by Ohfune *et al* in 1990, who also reported the first total synthesis thereby confirming its structure and absolute configuration.[2] The potent biological activity and impressive array of functionalities present in galantinic acid makes it an attractive target for synthesis. Interestingly, both the reported syntheses of **1**[2,3] suffer from poor selectivity in the *anti* -1,3-diol formation step, prompting us to undertake the current investigation, the details of which are reported in this communication.

As per the retrosynthesis (Scheme 1), we envisaged that, the *syn*-1,2-amino alcohol unit as present in **1** can be easily assembled, following a known protocol,[4] involving chelation controlled addition of a suitable Grignard reagent to an L-serinal derivative to afford the functionalized derivative **3**. The alkene group of **3** can then be utilized towards formation of the pivotal β-ketoester **2**. Finally, the chiral secondary hydroxy group directed stereoselective reduction of the ketone *via* intramolecular hydride delivery (Evans' protocol)[5] will result in the required *anti* -1,3-diol framework of the target molecule.

Scheme 1



1 (Galantinic acid) **2** **3** **4** (L-Serine)

R = ^{t}BuPh$_2$Si

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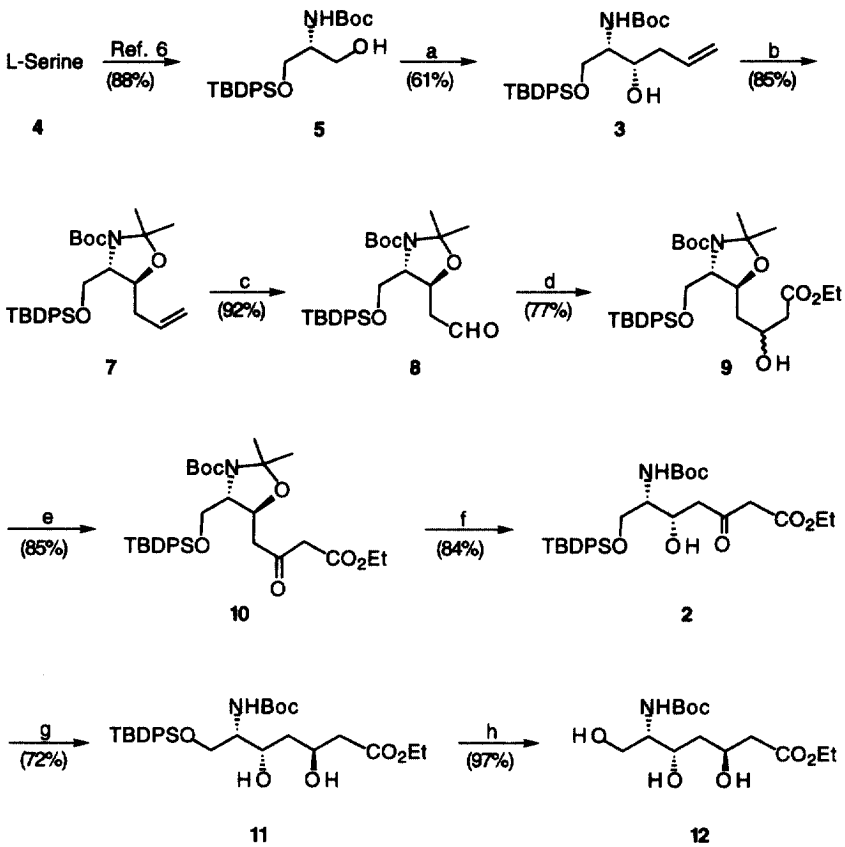
Accordingly, readily available L-serine (**4**) was converted to the aminodiol derivative **5** (Scheme 2) following a reported procedure.[6] Swern oxidation of **5** and *in-situ* reaction of the resulting aldehyde with allylmagnesium bromide, following an established protocol,[7] provided the expected *syn*-1,2-amino alcohol **3** (*syn* : *anti* > 95 : 5) in accordance with the earlier observations.[4,7,8] Protection of the aminoalcohol unit as its acetonide derivative **7**, followed by oxidative degradation of the alkene functionality afforded the corresponding aldehyde **8** in high overall yield. Introduction of the proposed β-ketoester moiety was achieved in a

Scheme 2



a. Swern oxidn. then $H_2C{=}CH\text{-}CH_2MgBr$. **b.** $Me_2C(OMe)_2$, PPTS. **c.** OsO_4, NMO then $NaIO_4$ (impregnated on silica gel). **d.** $BrZnCH_2CO_2Et$, Et_2O. **e.** PDC, CH_2Cl_2. **f.** aqueous 80% AcOH . **g.** $NaB(OAc)_3H$, CH_3CN, AcOH, -20°C. **h.** Bu_4NF, THF.

two-step sequence *via* initial Reformatsky reaction of **8** with ethyl bromozincacetate forming the hydroxyester **9** (as a 3:2 mixture of diastereoisomers at the newly created centre, by HPLC), followed by oxidation of the hydroxy group to the corresponding ketone **10**. Removal of the acetonide protection resulted in the key β-hydroxy ketone **2**, the strategically located chiral hydroxy group of which represents a convenient tool for stereoselective reduction of the proximal ketone. Thus, reduction of **2** with sodium triacetoxyborohydride

following Evans' protocol,[5] cleanly afforded the *anti* -1,3-diol **11** (92:8, by HPLC) in good yield. Finally, deprotection of the silylether linkage under standard conditions culminated in the target galantinic acid derivative **12**.[9]

In conclusion, a concise stereoselective route has been developed for the intended synthesis of the biologically important title amino acid in good overall yield (16%), starting from the readily available natural amino acid L-serine. The strategy and the approach described demonstrates the utility of chelation-controlled Grignard reaction on chiral α-amino aldehydes towards stereoselective formation of *syn*-1,2-amino alcohol unit. Also, by an efficient application of the β-hydroxy group directed reduction of a ketone, the *anti*-1,3-diol unit of the target skeleton could be easily assembled in a highly selective manner, an improvement upon the previously reported syntheses.

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References and Notes

IICT communication No. 4163

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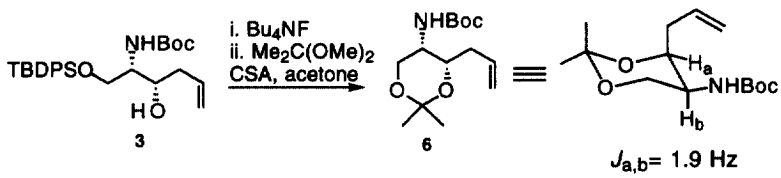
8. Assignment of *syn*-stereochemistry to the product **3**, initially based on analogy (ref. 4, 7), was proved conclusively by converting **3** to its diol acetonide **6**, whereupon the coupling constant between the two methine protons in the ring, $J_{a,b}$ = 1.9 Hz, is indicative of their *syn*-relationship, thus confirming the assigned stereochemistry.



9. All the compounds synthesized were fully characterized by their IR, ^{1}H and ^{13}C NMR and mass spectral data. Selected data for some of the key compounds are given below :
3: $[\alpha]_D$ = +10.7 (c = 1, $CHCl_3$); IR (neat) 3445, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.45 (br s, 9H), 2.27 (m, 2H), 2.82 (br s, 1H), 3.5-3.86 (m, 3H), 4.08 (m, 1H), 5.11 (m, 3H), 5.85 (m, 1H), 7.4 (m, 6H), 7.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.8, 135.2, 129.9, 127.8, 117.8, 79.2,

71.6, 66.1, 53.7, 38.2, 28.3, 26.8, 25.5; HRMS (FAB+) calcd. for $C_{27}H_{40}NO_4Si$: 470.2727 (MH+); found 470.2761.

10: $[\alpha]_D$ = +12.7 (c = 0.6, $CHCl_3$); IR (neat) 1710, 1698, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.32 (m, 9H), 1.44 (s, 3H), 1.50 (br s, 6H), 2.85 (br s, 2H), 3.48 (s, 2H), 3.57-3.86 (m, 3H), 4.19 (q, *J* = 7.4 Hz, 2H), 4.66 (m, 1H), 7.40 (m, 6H), 7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 200.1, 166.9, 166.7, 135.5, 129.7, 127.7, 91.0, 79.9, 71.4, 61.5, 61.3, 49.9, 28.6, 28.3, 27.0, 26.8, 19.2, 14.1; HRMS (FAB+) calcd. for $C_{33}H_{48}NO_7Si$: 598.3155 (MH+); found 598.3164.

11: $[\alpha]_D$ = +7.6 (c = 0.8, $CHCl_3$); IR (neat) 3443, 1716, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.42 (br s, 9H), 1.52 (m, 2H), 2.49 (d, *J* = 5.6 Hz, 2H), 3.19 (br s, 1H, exchangeable with D_2O), 3.38 (br s, 1H, exchangeable with D_2O), 3.56 (br s, 1H), 3.81 (d, *J* = 4.7 Hz, 2H), 4.15 (q, *J* = 7.3 Hz, 2H), 4.3 (m, 2H), 5.17 (br d, *J* = 9.2 Hz, 1H), 7.35 (m, 6H), 7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 172.7, 156.2, 135.5, 129.9, 127.9, 79.8, 69.1, 66.2, 65.4, 60.7, 54.9, 41.5, 39.8, 28.4, 26.9, 19.2, 14.1; HRMS (FAB+) calcd. for $C_{30}H_{46}NO_7Si$: 560.3043 (MH+); found 560.3021.

12: $[\alpha]_D$ = +9.3 (c = 0.8, $CHCl_3$); IR (neat) 3389, 1715, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.49 (s, 9H), 1.50-1.82 (m, 2H), 2.07 (br s, 1H, exchangeable with D_2O), 2.26 (s, 1H, exchangeable with D_2O), 2.52 (d, *J* = 5.4 Hz, 2H), 3.52 (br s, 1H), 3.75 (m, 2H), 4.22 (m, 4H), 5.32 (br d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.7, 156.6, 79.8, 68.2, 65.4, 63.9, 60.8, 55.6, 41.6, 39.9, 28.4; MS (FAB+) 344 (M^+ + Na), 322 (MH+).