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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 12.3 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.



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



a. Swern oxidn. then H₂C=CH-CH₂MgBr. b. Me₂C(OMe)₂, PPTS. c. OsO₄, NMO then NaIO₄ (impregnated on silica gel). d. BrZnCH₂CO₂Et, Et₂O. e. PDC, CH₂Cl₂. f. aqueous 80% AcOH . g. NaB(OAc)₃H, CH₃CN, AcOH, -20°C. h. Bu₄NF, 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

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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, ¹H and ¹³C NMR and mass spectral data. Selected data for some of the key compounds are given below :
3: [α]_D = +10.7 (c = 1, CHCl₃); IR (neat) 3445, 1693 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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, CHCl₃); IR (neat) 1710, 1698, 1686 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₃H₄₈NO₇Si : 598.3155 (MH+); found 598.3164.

11: $[\alpha]_D = +7.6$ (c = 0.8, CHCl₃); IR (neat) 3443, 1716, 1690 cm⁻¹; ¹H NMR (CDCl₃) 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 D₂O), 3.38 (br s, 1H, exchangeable with D₂O), 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); ¹³C NMR (CDCl₃) 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 C₃₀H₄₆NO₇Si : 560.3043 (MH+); found 560.3021.

12: $[\alpha]_D = +9.3$ (c = 0.8, CHCl₃); IR (neat) 3389, 1715, 1691 cm⁻¹; ¹H NMR (CDCl₃) 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 D₂O), 2.26 (s, 1H, exchangeable with D₂O), 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); ¹³C NMR (CDCl₃) 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⁺).