

TOTAL SYNTHESIS OF (+)-GALANTINIC ACID

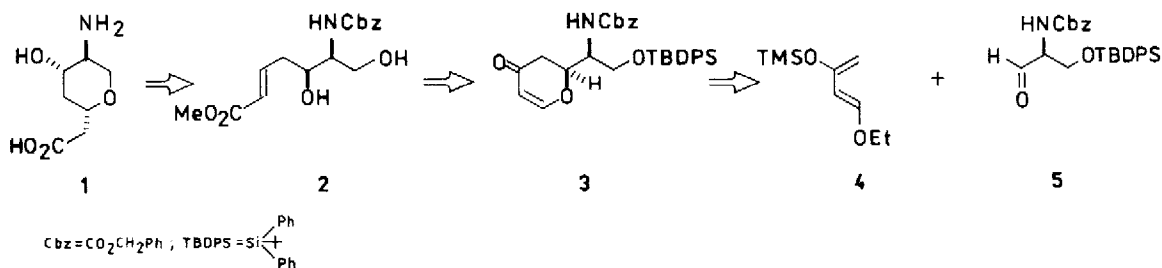
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Abstract - *N,O*-Protected L-serinal (5) afforded with diene 4, pyrone 3 as a single product which was transformed into (+)-galantinic acid derivative 8.

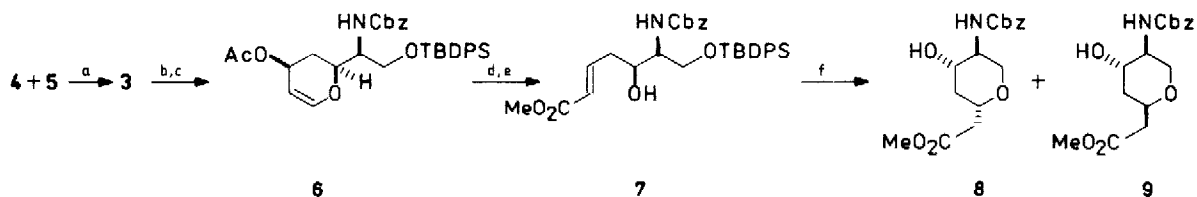
Galantin I is an antibiotic isolated from a culture broth of *Bacillus pulvifaciens* by Shoji et al.¹ The total synthesis of (+)-galantinic acid (1), an important component of galantin I, has been recently published.² Japanese authors have observed that the required pyran-ring system could be obtained *via* basic cyclisation³ of ester 2 which was synthesized using regioselective epoxide-ring opening with divinyl cuprate.²

A few years ago we have started long-term studies on the application of optically pure α -amino aldehydes in the total syntheses of natural products.⁴⁻⁸ During these studies we have observed that 4-amino-4-deoxy pentoses can be easily obtained from L- or D-serine derived aldehydes.⁹ A similar approach could be applied to the synthesis of (+)-galantinic acid (1), starting from *N,O*-protected L-serinal 5 (Scheme 1).



Scheme 1

In this communication we present the total synthesis of (+)-galantinic acid (1) with the use of Danishefsky's diene 4 and *N*-carbobenzyloxy-*O-tert*-butyldiphenylsilyloxy-L-serinal (5). In this approach, achievement of high diastereoselectivity of the (4+2)cycloaddition step was crucial. According to our earlier results,¹⁰⁻¹² pyrone 3 was expected to be the major product. Indeed, *N,O*-protected serinal 5, synthesized in a three-step procedure,⁵ afforded, with diene 4, pyrone 3 as a single product (Scheme 2). Luche-type reduction¹³ of pyrone 3 and protection of the hydroxy group of the intermediate alcohol gave acetate 6 in very high yield. The subsequent dihydropyran-ring opening reaction¹⁴ followed by Corey's oxidation¹⁵ afforded ester 7. Removal of the protecting silyloxy group from ester 7, followed by the earlier described cyclisation,^{2,3} produced a chromatographically separable 1:1 mixture of (+)-galantinic acid derivative 8,^{16,17} and its C-3 epimer 9.



Scheme 2. Reagents and reaction conditions: (a) $ZnBr_2$, THF, RT, 48 h, 86%; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, $-78^\circ C$, 3 h, 92%; (c) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , RT, 0.5 h, 95%; (d) $HgSO_4$, 5 mM H_2SO_4 aq-dioxane, RT, 24 h, 80%; (e) $NaCN$, AcOH, MnO_2 , MeOH, RT, 48 h, 68%; (f) K_2CO_3 , MeOH, RT, 24 h, 75%.

This total synthesis is a practical alternative to the known procedure.² Moreover, it exemplifies the usefulness of *N*-protected α -amino aldehydes in the synthesis of natural products.

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- For all compounds, elemental analyses and spectroscopic data were satisfactory. Selected data of new compounds:
 - mp $138-9^\circ C$; $[\alpha]_D^{25} -14.9^\circ$ (c 1, $CHCl_3$); 1H NMR (500 MHz), δ : 7.65-7.30 (m, 15 H), 7.21 (d, $J=6.0$ Hz, 1 H), 5.41 (dd, $J=6.0, 1.0$ Hz, 1 H), 5.09 (bs, 2 H), 4.87 (d, $J=9.7$ Hz, 1 H), 4.76 (bd, $J=14.9$ Hz, 1 H), 4.03 (m, 1 H), 3.78 (m, 2 H), 2.74 (dd, $J=16.8, 15.2$ Hz, 1 H), 2.38 (dd, $J=16.8, 2.3$ Hz, 1 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz), δ : 162.2, 135.5, 132.7, 130.0, 129.9, 128.6, 128.3, 128.2, 127.9, 127.8, 107.5, 67.2, 62.1, 54.2, 38.8, 26.8, 19.2.
 - mp $131-2^\circ C$; $[\alpha]_D^{25} +14.4^\circ$ (c 1, $CHCl_3$); 1H NMR (500 MHz), δ : 7.75-7.20 (m, 15 H), 6.36 (d, $J=6.1$ Hz, 1 H), 5.58-5.38 (m, 1 H), 5.21-5.00 (m, 3 H), 4.90 (d, $J=9.7$ Hz, 1 H), 4.76 (d, $J=6.1$ Hz, 2 H), 4.36 (bd, $J=12.1$ Hz, 1 H), 4.05-3.90 (m, 1 H), 3.75-3.60 (m, 2 H), 2.25-2.15 (m, 1 H), 2.04 (s, 3 H), 2.00-1.80 (m, 1 H), 1.06 (s, 9 H).
 - mp $126-7^\circ C$; $[\alpha]_D^{25} +2.6^\circ$ (c 1.16, $CHCl_3$); 1H NMR (500 MHz), δ : 7.40-7.30 (m, 5 H), 5.11 (s, 2 H), 4.64 (bs, 1 H), 4.05 (dd, $J=11.3, 4.6$ Hz, 1 H), 3.84-3.78 (m, 1 H), 3.69 (s, 3 H), 3.60-3.50 (m, 2 H), 3.11 (bt, $J=10.5$ Hz, 1 H), 2.80 (bs, 1 H), 2.60 (dd, $J=15.6, 7.9$ Hz, 1 H), 2.45 (dd, $J=15.5, 5.05$ Hz, 1 H), 2.12 (ddd, $J=12.8, 4.4, 1.9$ Hz, 1 H), 1.44 (dd, $J=23.8, 11.2$ Hz, 2 H).
 - mp $123-4^\circ C$; $[\alpha]_D^{25} +12.4^\circ$ (c 2.52, $CHCl_3$); 1H NMR (500 MHz), δ : 7.40-7.30 (m, 5 H), 5.43 (bd, $J=7.3$ Hz, 1 H), 5.13-5.05 (m, 2 H), 4.21-4.15 (m, 1 H), 4.07 (bs, 1 H), 3.68 (s, 3 H), 3.67 (m, 1 H), 3.55 (bd, $J=6.7$ Hz, 1 H), 2.58 (m, 1 H), 2.47 (dd, $J=15.2, 8.1$ Hz, 1 H), 2.38 (dd, $J=15.5, 4.8$ Hz, 1 H), 1.80-1.60 (m, 2 H).
- For comparison, compound 8 was transformed into NH-Boc form: mp $108-9^\circ C$ (lit.² mp $104-6^\circ C$); $[\alpha]_D^{25} -5.4^\circ$ (c 0.8, $CHCl_3$), (lit.² $[\alpha]_D^{25} -4.4^\circ$ (c 1.2, $CHCl_3$)); 1H NMR spectrum was identical with the reported one.²

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