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Enantioselective synthesis of (−)-galantinic acid

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Abstract—An efficient enantioselective synthesis of (−)-galantinic acid **1**, a non-proteogenic amino acid is described using Sharpless asymmetric epoxidation, dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfite as the key steps.

(−)-Galantinic acid **1** is a component of the peptide antibiotic galantin I, isolated from a culture broth of *Bacillus pulvifaciens*.[1] The original structure of galantin I was assigned after the synthesis of its unusual constituent amino acids, galantinic acid **1** and galantinamic acid **3**. The originally proposed structure of (−)-galantinic acid **2** was later revised to **1** by Sakai and Ohfune[2] who also reported its first total synthesis.[3] (Fig. 1) Galantinic acid has been a synthetic target of considerable interest due to its potent biological activity and unique structure with an array of functionalities. Various methods for its synthesis have been documented in the literature.[4] Most of these approaches employ chiral pool starting materials. Very recently, Raghavan and Ramakrishna Reddy[5] reported the stereoselective synthesis of (−)-galantinic acid using a sulfinyl moiety as an internal nucleophile through 1,3-asymmetric induction. As part of our research programme aimed at developing enatioselective synthesis of naturally occurring amino alcohols[6] and lactones,[7] the Sharpless asymmetric dihydroxylation and subsequent transformation of the diols formed via cyclic sulfites/sulfates were envisioned as powerful tools offering considerable opportunities for synthetic manipulations. Herein we report a new and highly enantioselective syntheses of (−)-galantinic acid employing the Sharpless asymmetric epoxidation and dihydroxylation procedures as the source of chirality.

The synthesis of (−)-galantinic acid **1** started from commercially available 1,3-propanediol **4** as illustrated in Scheme 1. The mono hydroxyl protection of **4** with *p*-methoxybenzyl chloride in the presence of NaH gave **5** in 86% yield. Compound **5** was oxidized to the aldehyde and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in THF at room temperature to furnish the Wittig product **6** in 81% yield. The reduction of olefinic ester **6** to the corresponding allylic alcohol **7** was achieved with DIBAL-H at 0 °C–rt in excellent yield. Compound **7** was then treated with titanium tetraisopropoxide and *t*-butyl hydroperoxide in the presence of (−)-DIPT under the Sharpless asymmetric epoxidation reaction conditions[8] to give the epoxide **8**[9] in good yield. The *trans*-selective opening of the epoxide **8**[10] was accomplished using perchloric acid and 60% DMSO to afford the triol, which was subsequently protected with benzaldehyde dimethyl acetal in the presence of a catalytic amount of DMAP to afford a mixture of 1,3- and 1,2-benzylidene derivatives in a 9:1 ratio. The desired major 1,3-benzylidene compound **9** was separated by silica gel column chromatography, which was found to be enantiomerically pure as determined by converting its free hydroxy group into the Mosher salt and analyzing the ^{1}H NMR spectrum.

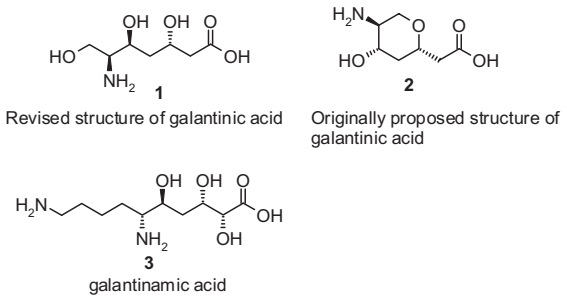

Figure 1.

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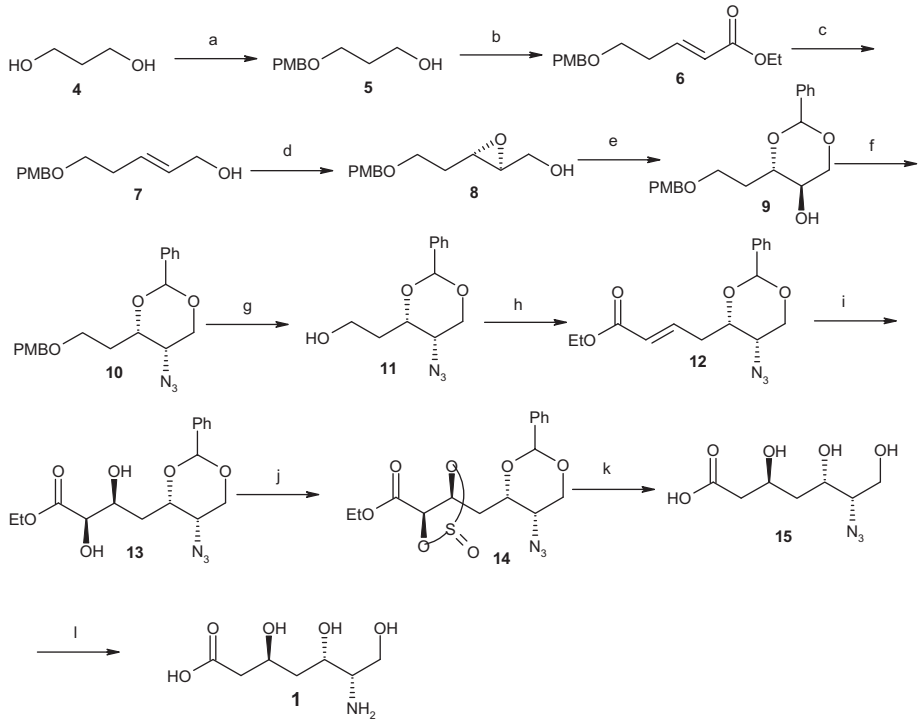

Scheme 1. Reagents and conditions: (a) *p*-$CH_3OC_6H_5CH_2Cl$, NaH, dry DMF, rt, 6 h, 86%; (b) (i) PCC, anhyd CH_3COONa, dry CH_2Cl_2, 0 °C– rt, 6 h; (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 81%; (c) DIBAL–H, dry CH_2Cl_2, 0 °C–rt, 2 h, 92%; (d) Ti(OPr-*i*)$_4$, (−)-DIPT, *t*-BuOOH, dry CH_2Cl_2, −25 °C, 36 h, 72%; (e) (i) 60% DMSO, $HClO_4$, 0 °C, 3 h, 89%; (ii) $C_6H_5CH(OMe)_2$, DMAP (cat), dry CH_2Cl_2, rt, overnight, 65%; (f) (i) MsCl, Et_3N, dry CH_2Cl_2, 5 h, 83%; (ii) NaN_3, dry DMF, 78%; (g) DDQ, dry CH_2Cl_2, rt, 3 h, 91%; (h) (i) PCC, anhyd CH_3COONa, dry CH_2Cl_2, rt, 6 h; (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 83%; (i) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_3FeCN_6, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0 °C, 87%; (j) $SOCl_2$, Et_3N, 30 min, 89%; (k) (i) $NaBH_4$, dry THF, MeOH; (ii) 4 N H_2SO_4, 2 h, rt, 77%; (l) 10% Pd/C, H_2, MeOH, rt, 88%.

At this stage an attempt to convert the free hydroxyl group of **9** to azide under Mitsunobu conditions was not very satisfactory. Accordingly the free hydroxyl group of **9** was converted into *O*-mesylate, which on nucleophilic displacement with sodium azide in dry DMF afforded compound **10**[11] in 78% yield. The *p*-methoxy benzyl-protecting group was cleaved by treating **10** with DDQ to furnish the alcohol **11** in excellent yield.

The PCC oxidation of **11** to the aldehyde and subsequent reaction with (ethoxycarbonylmethylene)triphenylphosphorane gave the olefin **12** in 83% yield. The dihydroxylation of olefin **12** with osmium tetroxide and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQ)_2PHAL$ as the chiral ligand under the Sharpless asymmetric dihydroxylation conditions[12] furnished the diol **13**[13] in excellent yield. The diol **13** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **14**[14] in 89% yield. The essential feature of the synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of the cyclic sulfite **14** would occur in a regiospecific manner at the α-carbon atom. Indeed, the cyclic sulfite **14** reacted with one equivalent of $NaBH_4$ with apparent complete selectivity for attack at C-2, the α-position, to furnish the intermediate sulfite ester which, without further isolation was subjected to acidic hydrolysis using 4 N H_2SO_4 to give **15** in good yield. Reduction of the azide under hydrogenation conditions using 10% Pd/C in methanol furnished (−)-galantinic acid **1** in 88% yield, $[\alpha]_D^{25}$ −29.7 (lit.[3] $[\alpha]_D^{25}$ −29.4). The physical and spectroscopic data of **1** are in full agreement with the literature data.[3]

In conclusion, a practical and enantioselective synthesis of (−)-galantinic acid has been achieved using Sharpless asymmetric epoxidation and dihydroxylation and through regioselective nucleophilic opening of a cyclic sulfite. The synthetic strategy described has significant potential for further extension to other isomers and related analogues including galantinamic acid **3**, the other component of galantin I. Currently, studies are in progress in this direction.

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11. Spectral data of compound **10**: $[\alpha]_D^{25}$ −4.39 (*c* 0.22, $CHCl_3$); IR (neat): 2104, 1612, 1513, 1465, 1362, 1248, 1216; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.37$–7.42 (m, 5H), 7.29 (d, $J = 10$ Hz, 2H), 6.87 (d, $J = 10$ Hz, 2H), 5.50 (s, 1H), 4.54 (s, 2H), 4.40–4.52 (m, 2H), 4.32–4.34 (m, 1H), 3.88 (td, $J = 8.71$, 3.21, 1H), 3.73 (t, $J = 3.67$ Hz, 2H), 3.70 (s, 3H), 1.76–1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 29.67$, 31.58, 38.26, 55.22, 64.62, 69.00, 72.25, 72.74, 75.63, 101.13, 113.77, 126.04, 128.24, 129.19, 129.49, 159.22; GC–MS: 369 (M+), 357.05, 331.05, 279.05, 261.05, 241.05, 200.05, 172.04. Anal. Calcd for $C_{20}H_{23}N_3O_4$ (369.42) C, 65.03%, H, 6.28%, N, 11.37%. Found C, 64.90%, H, 6.21%, N, 11.26%.
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13. The diastereomeric excess was found to be 91% using ^{13}C NMR analysis. Spectral data of compound **13**: $[\alpha]_D^{25}$ −3.28 (*c* 0.80, $CHCl_3$) IR (neat): 3561, 2112, 1716, 1522, 1343, 1218, 1210; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.25$–7.32 (m, 5H), 5.51 (s, 1H), 4.21–4.25 (m, 1H), 4.13 (d, $J = 8$ Hz, 1H), 4.06 (q, $J = 6$ Hz, 2H), 4.22 (q, $J = 8$ Hz, 1H), 3.62–3.74 (m, 2H), 3.06 (t, $J = 4$ Hz, 2H), 3.54–3.56 (m, 1H), 2.06 (br, 2H), 0.93 (t, $J = 9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 13.75$, 22.02, 25.26, 29.23, 32.94, 54.85, 60.91, 69.40, 72.20, 78.67, 113.37, 128.84, 158.73, 170.56. Anal. Calcd for $C_{16}H_{21}N_3O_6$ (351.38) C, 54.70%, H, 6.03%, N, 11.96%. Found C, 54.62%, H, 5.98%, N, 11.99%.
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