# Stereocontrolled Total Synthesis of Galactostatin from Serine

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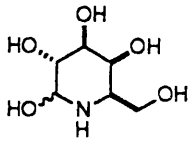
An efficient stereoselective total synthesis of (−)-galactostatin (−)-**1** from *N-tert*-butoxycarbonyl-2,3-isopropylidene L-serine methyl ester (21% overall yield) is described *via* thiazole intermediates serving as protected aldehydes; the parallel synthesis of the natural antipole (+)-**1** starts from D-serine.

The synthesis of polyhydroxypiperidines (aza sugars) is of current interest since these sugar analogues in which the ring oxygen is replaced by the NH group have been shown to possess potent and specific inhibitory activity against the hydrolysis of the corresponding glycosides by specific enzymes.[1] (+)-Galactostatin† (+)-**1**, a strong inhibitor of several β-galactosidases,[2] has recently been isolated[3] from the culture broth of *Streptomyces lydicus* PA-5725 and its absolute

† Also named *galacto*-nojirimycin. See ref. 2 and 5.

configuration established[4] by total synthesis (*ca.* 6.5%) from a chiral building block derived from L-tartaric acid. Synthetic (+)-**1** obtained from α-D-glucofuranose diacetonide was described earlier.[5] We report herein a new approach to the synthesis of galactostatin in either antipodal form, (+)-**1** and (−)-**1**, employing thiazole derivatives[6] as convenient homologating reagents of D- and L-serine to C-4 and C-6 amino aldehydes. The synthetic strategy is summarized in Scheme 1 (only the L-stereochemical series is shown).

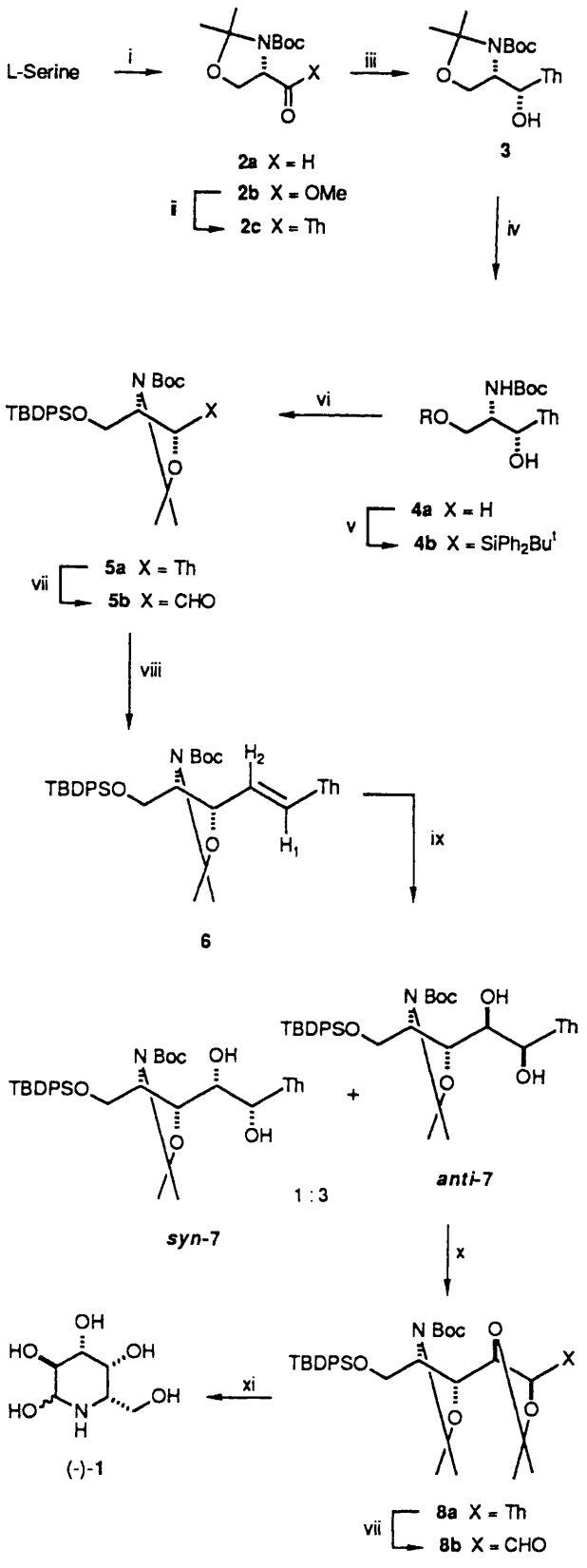
We employed a novel and straightforward route for the one-carbon chain elongation of L-serine which avoids the intermediate amino aldehyde[7] **2a**. In this new procedure the activated intermediate is the thiazolyl amino ketone **2c**‡ which is obtained directly from the L-serine derived methyl ester[8] **2b** by substitution with 2-lithiothiazole (92%). The spectral and physical properties (NMR and $[\alpha]_D$) of **2c** were in good accord with those of the compound obtained by a different route.[9] As reported,[9] the highly diastereoselective (ds) reduction (ds ⩾ 95%) of the carbonyl of **2b** by sodium borohydride afforded the *syn* amino alcohol **3** in essentially quantitative yield. The acetonide group in **3** was removed and the primary hydroxy group in the resulting diol **4a** (85%) was selectively silylated to give **4b** (96%), the acetonization of which afforded the fully protected amino alcohol **5a** (90%). This compound was readily converted to the aldehyde **5b** (81%) by the standard thiazole-to-formyl deblocking protocol.[7] The Wittig alkenation of **5b** with thiazolylmethylenetriphenylphosphorane (2-TMP)[10] occurred in high yield (92%) and complete selectivity leading exclusively to the desired *E*-alkene **6** ($J_{H1H2}$ 16 Hz). The *cis* dihydroxylation of **6** using a catalytic amount of osmium tetroxide with 2 equiv. of *N*-methylmorpholine *N*-oxide as reoxidant ($OsO_4$/NMO) in tetrahydrofuran-*tert*-butyl alcohol–water, afforded a 3 : 1 mixture of 1,2-diols *anti*-**7** and *syn*-**7** (total yield 83%) from which the major isomer having the assumed *anti*-configuration[11] was isolated by chromatography (silica, hexane–diethyl ether, 40 : 60) in 62% yield. After protection of the diol *anti*-**7** as the acetonide derivative **8a** (quantitative), the aldehyde **8b** [73%, IR ($CHCl_3$) 1725 ν/cm$^{-1}$] was liberated from the thiazole ring by the standard procedure.[7] The one-pot removal of all protecting groups in crude **8b** by treatment with aqueous trifluoroacetic acid gave galactostatin (−)-**1** (92%) as a colourless amorphous powder showing physical properties {m.p. 94–96 °C, $[\alpha]_D^{20}$ = −85.7° (*c* 0.40, $H_2O$)} almost identical except for the sign of the optical rotation, with those of synthetic and natural galactostatin (+)-**1** {m.p. 93–95 and 94–98 °C, $[\alpha]_D^{25}$ = +84.6° (*c* 0.3, $H_2O$), $[\alpha]_D^{23}$ = +85.6° (*c* 1.0, $H_2O$)}.[4]




(+)-1

‡ All new compounds showed consistent NMR and IR spectral data with the assigned structure and gave satisfactory elemental analyses.

*Selected data*: **2c**: $[\alpha]_D^{20}$ = −69.8° (*c* 1.02, $CHCl_3$). **3**: $[\alpha]_D^{20}$ = −2.83° (*c* 1.06, $CHCl_3$). **4a**: $[\alpha]_D^{20}$ = −2.10° (*c* 0.2, $CHCl_3$). **4b**: $[\alpha]_D^{20}$ = +2.90° (*c* 0.87, $CHCl_3$). **5a**: $[\alpha]_D^{20}$ = −11.8° (*c* 0.93, $CHCl_3$). **5b**: $[\alpha]_D^{20}$ = +6.30° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1730 ν/cm$^{-1}$; $^1$H NMR (80 MHz, $CDCl_3$, 340 K) δ 1.02 (s, 9 H), 1.43 (s, 9 H), 1.56 (bs, 6 H), 3.72 (dd, 1 H, *J* 10.2, 6.5 Hz), 3.86 (dd, 1 H, *J* 10.2, 4.3 Hz), 4.31 (ddd, 1 H, *J* 6.5, 4.3, 3.2 Hz), 4.60 (dd, 1 H, *J* 3.2, 0.8 Hz), 7.30 (m, 6 H), 7.60 (m, 4 H), 9.72 (d, 1 H, *J* 0.8 Hz). **6**: $[\alpha]_D^{20}$ = −6.10° (*c* 0.92, $CHCl_3$). *syn*-**7**: $[\alpha]_D^{20}$ = +9.6° (*c* 0.95, $CHCl_3$). *anti*-**7**: $[\alpha]_D^{20}$ = +17.1° (*c* 0.96, $CHCl_3$). **8a**: $[\alpha]_D^{20}$ = +19.0° (*c* 1.45, $CHCl_3$), $^1$H NMR (80 MHz, $CDCl_3$, 340 K) δ 1.03 (s, 9 H), 1.39 (s, 9 H), 1.48 (bs, 6 H), 1.50 (bs, 6 H), 3.81 (m, 2 H), 4.18 (ddd, 1 H, *J* 6.4, 5.23, 3.5 Hz), 4.50 (dd, 1 H, *J* 4.9, 6.4 Hz), 4.62 (dd, 1 H, *J* 4.9, 3.8 Hz), 5.30 (d, 1 H, *J* 3.8 Hz), 7.25 (d, 1 H, 3.2 Hz), 7.30 (m, 6 H), 7.60 (m, 4 H), 7.76 (d, 1 H, *J* 3.2 Hz).




**Scheme 1** Th = 2-thiazolyl. *Reagents and conditions*: i, see ref. 8; ii, ThLi (from ThBr and Bu$^n$Li at −78 °C), $Et_2O$, −50 °C, 5 h; iii, $NaBH_4$, MeOH, −60 °C, 1 h; iv, 0.5 mol dm$^{-3}$ $CF_3CO_2H$, $CH_2Cl_2$, room temp., 15 min; v, Bu$^t$$Ph_2SiCl$, $Et_3N$, DMAP, DMF, room temp., 16 h; vi, DMP, TsOH (cat.), $C_6H_6$, heat, 24 h; vii, see ref. 7; viii, $Ph_3P$=CH–Th, $C_6H_6$, room temp., 16 h; ix, $OsO_4$ (cat.), NMO, THF–Bu$^t$OH–$H_2O$, room temp., 16 h; x, DMP, TsOH(cat.), $Me_2CO$, $MgSO_4$, room temp., 4 h; xi, aq. $CF_3CO_2H$ (80%), room temp., 0.5 h

The entire sequence to (−)-**1** from the L-serine derived methyl ester ***2b*** requires eleven steps and provides the product in 21% overall yield. The same sequence can be employed for the preparation of the natural enantiomer (+)-**1** starting from commercially available D-serine. This new route to the enantio-couple (+)- and (−)-galactostatin from the two serine antipods offers the opportunity for numerous stereochemical variations, which should provide access to various compounds of the same family.

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