(+)-6a or (+)-6b in 2 mL of THF at −78 °C followed by warming to 0 °C for 1.5 h. After quenching with 0.5 mL of saturated NH_4I solution, washing, and drying, the α-hydroxy carbonyl compounds were isolated by preparative TLC (silica gel G) eluting with 1:1 *n*-pentane/ether for 2-hydroxy-1-phenylpropanone and methyl 2-hydroxy-2-phenylpropanoate and with $CHCl_3$ for 2-hydroxy-2-methyl-1-tetralone. Products were identified by comparison of their spectral properties with those of authentic samples and their ee's and configurations determined as previously described.[1,7]

X-ray Analysis of (+)-3-(2*R*,3*S*)-[*o*-(*S*)-(2-Methylbutoxy)phenyl]-1,2-benzisothiazole 1,1-Dioxide Oxide (6b). Data were collected on an Enraf-Nonius CAD4 diffractometer using a crystal of dimensions of 0.42 × 0.26 × 0.14 mm. Crystal data: $C_{18}H_{19}NO_4S$, M_r 345.4230, orthorhombic, $P2_12_12_1$, a = 8.489 (1) Å, b = 14.429 (1) Å, c = 14.570 (2) Å, V = 1784.7 Å^3, Z = 4, D_{calcd} = 1.286 g cm^{-3}, λ(Cu Kα) = 1.541 84 Å, μ = 17.5 cm^{-1}. Lattice parameters were determined from 25 reflections with 22° ≤ 2θ ≤ 62°; 2125 reflections were measured by the ω−2θ scan technique with 4° ≤ 2θ ≤ 150°. Intensities of three standard reflections (302, 211, 040) recorded every 3500 s of X-ray exposure showed no significant decay. A total of 1578 unique, observed reflections with $I > 3\sigma(I)$ were used during structure refinement. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by MULTAN 11/82.[21] Hydrogen atoms were found from subsequent difference Fourier syntheses. Refinement by full-matrix least squares to minimize $\sum w(|F_o| - |F_c|^2)$ led to R = 0.060 and R_w = 0.082 for 218 variables with $w = 1/\sigma^2$. The maximum least-squares shift to esd ratio was 0.01 in the final refinement cycle. The largest residual electron density in the final difference map was +.30 e Å^{-3}. All computer programs were from the Enraf-Nonius SDP Package.[22]

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE 8502076) and the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 34014.

Supplementary Material Available: X-ray data including tables of atomic positional parameters, thermal parameters, bond distances, and bond angles for (+)-(2*R*,3*S*)-**6b** as well as proton NMR spectra for **5b** and *o*-(*S*)-(2-methylbutoxy)phenyl bromide (7 pages). Ordering information is given on any current masthead page.

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Total Syntheses of Galactosidase Inhibitors (+)-Galactostatin and (+)-1-Deoxygalactostatin[1]

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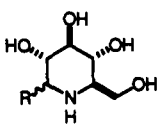
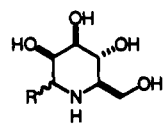
β-Galactosidase inhibitors, (+)-galactostatin and its 1-deoxy analogue (+)-deoxygalactostatin, have been synthesized by utilizing the allylic alcohol 7 as a common chiral building block.

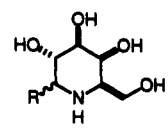
The antibiotics nojirimycin (**1**)[2-4] and 1-deoxynojirimycin (**2**),[4-6] the first representative naturally occurring azahexoses, are essentially D-glucose and its 1-deoxy analogue in which the ring oxygen is replaced by the NH group. Subsequently, the D-mannose analogues of **1** and **2**, mannojirimycin (**3**)[7] and 1-deoxymannojirimycin (**4**),[8,9] have been found in nature. These sugar analogues having



1, R = OH
2, R = H

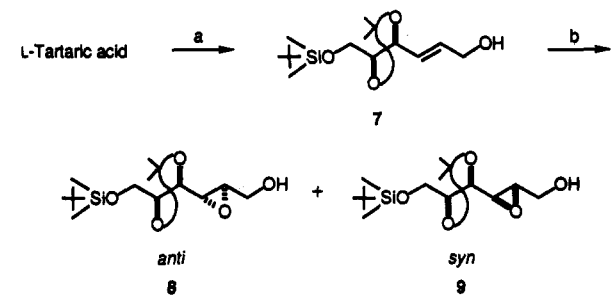


3, R = OH
4, R = H



5, R = OH
6, R = H

Scheme I[a]



[a] (a) Reference 15; (b) RCO_3H or t-BuO_2H, $VO(acac)_2$ (Table I).

nitrogen have been shown to be potent and specific inhibitors of the hydrolysis of the corresponding glycosides, D-glucosides and D-mannosides, by specific glycosidases. In an attempt to explore the potential of azapyranoses in studies of glycohydrolases, the basic analogues of D-galactose and its 1-deoxy derivative, i.e., **5** and **6**, respectively, have recently been synthesized from D-galactose[10] or D-glucose[11] and have been tentatively named *galacto-*

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Table I. Epoxidation of Allylic Alcohol 7

oxidant	conditions: time, h	conditions: temp, °C	yield,[a] %	syn:anti ratio[b]
m-CPBA	14	0	95	35:65
m-CPBA	48	−20	88	30:70
CH_3CO_3H	4	rt[c]	81	29:71
CF_3CO_3H	3	rt	41	12:88
t-BuO_2H–$VO(acac)_2$	3	80	50	32:68

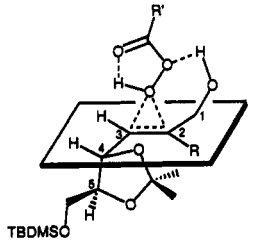
[a] Isolated yield. [b] Based on ^1H NMR integration. [c] Room temperature.

nojirimycin and *galacto*-1-deoxynojirimycin for convenience.[11] These studies have revealed that **5** and **6** are powerful and specific inhibitors of several α- and β-galactosidases, however, no chemical and physical characteristics of **5** were given in the reports.[10a,11] Immediately after these syntheses, the natural product **5** was found in the culture broth of *Streptomyces lydicus* PA-5725 by Miyake et al.[12] and named galactostatin. The relative configuration of galactostatin was completely determined from the ^1H NMR spectrum.[13] Natural (+)-galactostatin and its reduction product (+)-1-deoxygalactostatin (**6**) have been shown to display strong inhibitory activity toward several β-galactosidases.[12b,14]

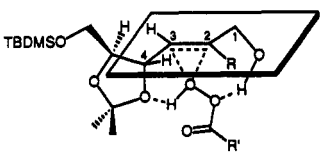
In this report we describe the enantioselective synthesis of (+)-galactostatin (**5**) and (+)-1-deoxygalactostatin (**6**) by utilizing a non-carbohydrate chiral building block, **7**, as a common starting material which has previously been used as a synthetic intermediate in the preparation of nojirimycin (**1**) and 1-deoxynojirimycin (**2**) in this laboratory.[15] Our synthesis establishes the absolute configuration of natural **5**.

The initial stage of our investigation focused on epoxidation of the allylic alcohol **7**, easily prepared from L-tartaric acid according to the procedure reported previously from this laboratory,[15] using various peracids or vanadyl acetylacetonate and *tert*-butyl hydroperoxide (Scheme I). The results are summarized in Table I.

Table I indicates that epoxidation of **7** in all cases showed an appreciable anti diastereomeric bias leading to **8**.[16] For the epoxidation with peracids (entries 1–4), one can anticipate two transition-state models A and B leading to the *anti*- and *syn*-epoxides **8** and **9**, respectively. The



A



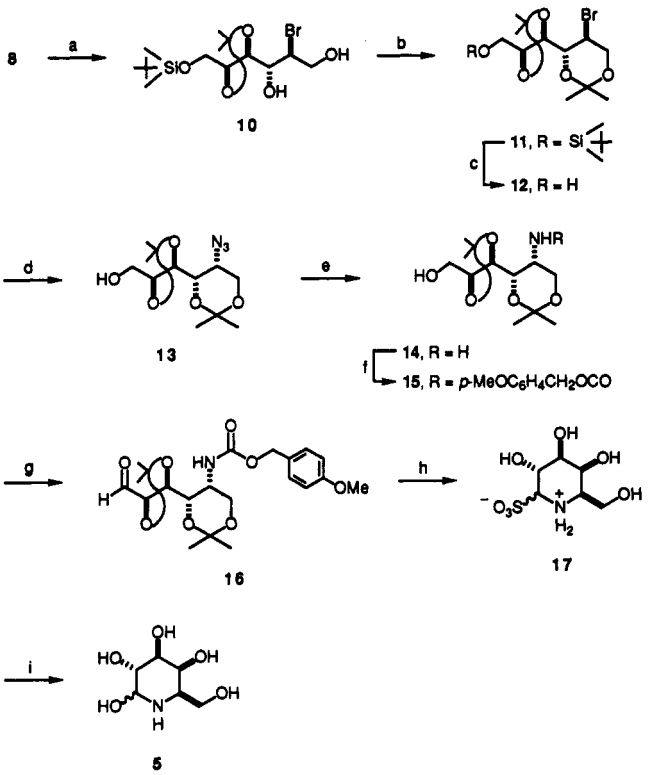
B

observed anti selectivity can be rationalized according to A where R = H. In this model, the conformation with the C-4–O bond (alkoxy) inside and the C-4–C-5 bond (alkyl) anti is stabilized due to the inside alkoxy effect[17] in which the developing bond forms trans to the alkyl group to permit an antiperiplanar approach. Alternative model B, which would give rise to syn selectivity, can be adaptable only when R = alkyl. This is suggested by the known examples[18] in which the direction of the steric course of *m*-CPBA epoxidations of allylic alcohols involves secondary interaction between the ether oxygen atom and the incoming peracid (cooperative effect). If R = alkyl, the transition state A would be destabilized owing to the severe $A^{(1,3)}$ interaction[19] between the 2-alkyl group and the 4-alkoxy group positioned in the plane of the carbon–carbon double bond. Indeed, it has been reported that, in the case of *trans*-allylic alcohols without alkyl substituents at the C-2 position, the degree of syn stereoselectivity is low[20] or none.[21]

A similar picture involving the inside alkoxy transition state A (R = H) may be drawn to rationalize the anti stereodifferentiation observed in the vanadium-catalyzed epoxidation with *tert*-butyl hydroperoxide (Table I, entry 5).

The desired *anti*-epoxide **8** thus obtained was first elaborated to (+)-galactostatin (**5**) according to the reaction sequence outlined in Scheme II. Regio- and stereoselective epoxide-opening of **8** was effected by treatment with dilithium tetrabromonickelate(II) (Li_2NiBr_4)[22] in THF to give the bromohydrin **10** in 74% yield. This was converted to the diacetonide **11** with acetone dimethyl acetal (re-

Scheme II[a]



[a] (a) Li_2NiBr_4, THF; (b) $(MeO)_2CMe_2$, TsOH·Py; (c) $(n\text{-}Bu)_4NF$, THF; (d) NaN_3, Me_2SO; (e) H_2, Pd–C, MeOH; (f) *p*-methoxybenzyl *S*-4,6-dimethylpyrimidin-2-yl thiocarbonate, Et_3N, dioxane; (g) $(COCl)_2$, Me_2SO, Et_3N (h) SO_2, H_2O; (i) Dowex 1-X8 (OH^-).

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(13) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 661.
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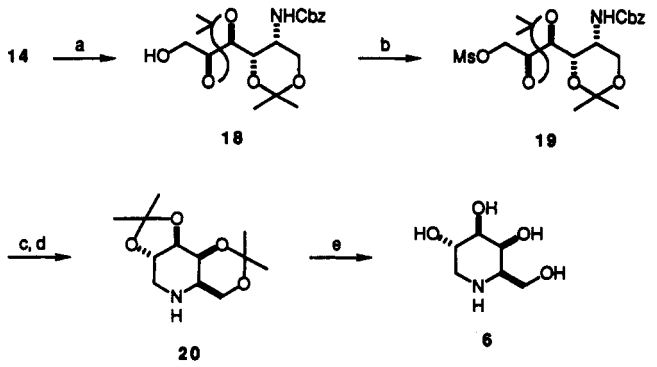
Scheme III[a]



[a] (a) CbzCl, aqueous Na_2CO_3, CH_2Cl_2; (b) MsCl, Et_3N, CH_2Cl_2; (c) H_2, Pd-C, MeOH; (d) Et_3N, MeOH; (e) HCl, MeOH.

fluxing acetone, TsOH·Py). Desilylation of **11** (*n*-Bu_4NF, THF) followed by reaction of the resulting alcohol **12** with sodium azide in dimethyl sulfoxide afforded the azide **13** as a single diastereomer, with inversion of the configuration at C-5, in 63% overall yield from **11**. After catalytic hydrogenation over palladium on carbon (82% yield), the resulting amine **14** was subjected to selective N-protection by treatment with *p*-methoxybenzyl *S*-4,6-dimethylpyrimidin-2-yl thiocarbonate[23] and triethylamine to give the carbamate **15** in 93% yield. Swern oxidation of **15** afforded the aldehyde **16** in 98% yield. Exposure of **16** to aqueous sulfurous acid at room temperature resulted in deprotection and formation of the bisulfite adduct to yield 1-deoxygalactostatin-1-sulfuric (galactostatin bisulfite adduct) (**17**) in 47% yield, whose spectral characteristics (^1H and ^{13}C NMR) were identical with those for naturally derived material. Subsequently, **17** was applied to a column of ion-exchange resin [Dowex 1-X8 (OH^-)] and eluted with water to furnish (+)-galactostatin (**5**) in 69% yield. Synthetic **5** had $[\alpha]^{25}_D$ +84.6° (*c* 0.3, H_2O), identical with that published for the natural product $[[\alpha]^{23}_D$ +85.6 ± 1.2° (*c* 1.0, H_2O)],[12b] and showed spectra (^1H and ^{13}C NMR and mass) identical with the corresponding authentic spectra of natural **5**.

With the amine **14** in hand, we next turned to elaborate this to (+)-1-deoxygalactostatin (**6**) as outlined in Scheme III. Thus, the amino group **14** was protected with benzyl chloroformate under alkaline conditions to give the carbamate **18** in near quantitative yield. Mesylation of **18** under standard conditions provided the mesylate **19** (96% yield). Hydrogenolysis in the presence of palladium on carbon in methanol followed by treatment with triethylamine afforded protected 1-deoxygalactostatin, i.e., **20**, in 57% yield from **19**. Deprotection with hydrochloric acid in methanol led to the formation of (+)-1-deoxygalactostatin (**5**) in 89% yield. The optical rotation and spectral data (^1H and ^{13}C NMR) of synthetic **5** were consistent with the reported values.[13]

In summary, we have achieved the enantioselective synthesis of (+)-galactostatin (**5**) and (+)-1-deoxygalactostatin (**6**) by utilizing the non-carbohydrate building block **7** as a common chiral synthon. Our synthesis establishes the absolute stereostructure of naturally occurring galactostatin.

Experimental Section

General Procedures. All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter in a 1-dm cell. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer. ^1H NMR spectra were run on a Bruker AM-400 (400 MHz) spectrometer. ^{13}C NMR spectra were determined on a Bruker AM-400 spectrometer at 100.6 MHz, and the degree of substitution of each carbon atom was determined by complete decoupling and DEPT composed 90° and 135° pulsed sequence experiments. ^1H chemical shifts are expressed relative to $CHCl_3$ at δ 7.26, and ^{13}C chemical shifts are expressed relative to $CDCl_3$ at δ 77.0, unless otherwise indicated. Mass spectra were obtained on a Hitachi RMU-7L double-focusing mass spectrometer at an ionizing potential of 70 eV. Analytical TLC was performed on Merck precoated silica gel 60 F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

Epoxidation of 6-[(*tert*-Butyldimethylsilyl)oxy]-4(*S*),5-(*S*)-(isopropylidenedioxy)-2(*E*)-hexen-1-ol (7). A. With *m*-Chloroperbenzoic Acid. To a stirred, cold (0 °C) solution of **7** (103 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) was added *m*-chloroperbenzoic acid (118 mg, 0.68 mmol), and the mixture was stirred at 0 °C for 14 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and neutralized with a saturated $NaHCO_3$ solution. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel with hexane–ethyl acetate (8:1) to provide a mixture of (2*R*,3*S*,4*R*,5*S*)- and (2*S*,3*R*,4*R*,5*S*)-6-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-4,5-(isopropylidenedioxy)hexan-1-ol (**8** and **9**, respectively). The reaction was also carried out at −20 °C for 48 h (see Table I). Separation of the mixture of **8** and **9** by MPLC [silica gel, 1.5 cm × 30 cm, hexane–ethyl acetate (10:1)] afforded **8** as a colorless oil: $[\alpha]^{25}_D$ +1.63° (*c* 1.5, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6 H, s), 0.90 (9 H, s), 1.41 (3 H, s), 1.42 (3 H, s), 1.90 (1 H, br dd, *J* = 7.2, 5.7 Hz), 3.18–3.20 (2 H, m), 3.68 (1 H, ddd, *J* = 12.7, 7.6, 4.0 Hz), 3.75 (1 H, dd, *J* = 10.7, 4.8 Hz), 3.78 (1 H, dd, *J* = 10.7, 4.0 Hz), 3.92–3.99 (3 H, m); ^{13}C NMR ($CDCl_3$) δ −5.38 (CH_3), −5.30 (CH_3), 18.41 (C), 25.96 (CH_3), 26.62 (CH_3), 26.90 (CH_3), 55.33 (CH), 56.17 (CH), 61.35 (CH_2), 63.55 (CH_2), 77.04 (CH), 79.12 (CH), 109.96 (C); MS *m/z* (relative intensity) 303 ($M^+ - CH_3$, 4), 147 (25), 109 (18), 105 (100), 76 (61). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.35; H, 9.45.

B. With Peracetic Acid. To a stirred and cooled (0 °C) solution of peracetic acid (1.32 mmol) in dilute acetic acid was added dropwise a solution of **7** (200 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) over 5 min, and the resulting mixture was allowed to warm to room temperature with stirring. After 4 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and neutralized with a saturated $NaHCO_3$ solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was worked up by procedure A. For the results, see Table I.

C. With Pertrifluoroacetic Acid. To a stirred, cooled (0 °C) solution of pertrifluoroacetic acid (2.94 mmol), prepared by the method of Emmons,[24] in CH_2Cl_2 was added dropwise a solution of **7** (600 mg, 1.98 mmol) in CH_2Cl_2 (20 mL) over 5 min. The mixture was allowed to warm to room temperature and stirred for 3 h. After neutralization with a saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was worked up by procedure A. For the results, see Table I.

D. With Vanadyl Acetylacetonate–*tert*-Butyl Hydroperoxide. To a solution of **7** (150 mg, 0.826 mmol) in benzene (5 mL) was added vanadyl acetylacetonate (2 mg, 0.008 mmol), and the mixture was refluxed. After 30 min, 2.8 mL of a 3 M solution of *tert*-butyl hydroperoxide (8.4 mmol) in 2,2,4-trimethylpentane was added to the mixture via syringe. After being refluxed for 3 h, the reaction mixture was diluted with benzene (10 mL), washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was worked up by procedure A. For the results, see Table I.

(2*S*,3*R*,4*S*,5*S*)-2-Bromo-6-[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)hexane-1,3-diol (10). A 0.4 M

(23) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269.

(24) Emmons, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 3468.

solution of dilithium tetrabromonickelate (7 mL, 2.80 mmol), prepared from nickel(II) bromide and lithium bromide,[22] in THF was added to a solution of 8 (469 mg, 1.47 mmol) in THF (4 mL), and the mixture was refluxed for 6 h. After cooling, 5 mL of a phosphate buffer solution (pH 7.0) was added to the reaction mixture, and the resulting mixture was stirred for 30 min and diluted with CH_2Cl_2 (100 mL). The organic phase was separated, washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel with hexane–ethyl acetate (8:1) gave **10** (437 mg, 74%) as a colorless oil: $[\alpha]^{25}_D$ −7.83° (*c* 0.5, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.42 (3 H, s), 1.44 (3 H, s), 1.67–1.70 (1 H, br m), 2.70–2.76 (1 H, br m), 3.71 (1 H, dd, *J* = 10.5, 6.0 Hz), 3.83 (1 H, dd, *J* = 10.5, 9.3 Hz), 3.91 (1 H, ddd, *J* = 9.5, 8.6, 0.8 Hz), 4.03–4.08 (3 H, m), 4.11 (1 H, ddd, *J* = 9.1, 5.3, 4.3 Hz), 4.41 (1 H, dd, *J* = 8.6, 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ −5.38 (CH_3), −5.33 (CH_3), 18.80 (C), 25.99 (CH_3), 26.75 (CH_3), 27.10 (CH_3), 54.96 (CH), 55.72 (CH), 60.67 (CH_2), 63.62 (CH_2), 78.17 (CH), 78.36 (CH), 109.95 (C); MS *m/z* (relative intensity) 385 ($M^+ + 2 - CH_3$, 4), 383 ($M^+ - CH_3$, 4), 267 (6), 265 (6), 245 (7), 131 (53), 75 (100).

(2*S*,3*R*,4*R*,5*S*)-5-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-2,3:4,6-bis(isopropylidenedioxy)hexane (11). To a solution of **10** (2.23 g, 5.58 mmol) in acetone (20 mL) was added 2,2-dimethoxypropane (5.83 g, 55.8 mmol), followed by pyridinium *p*-toluenesulfonate (140 mg, 0.56 mmol), and the resulting mixture was stirred at room temperature for 20 h and then at reflux for 2 h. After concentration in vacuo, the product was diluted with $CHCl_3$ (100 mL), washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane–ethyl acetate (8:1) to give **11** (1.62 g, 66%) as a pale yellow oil: $[\alpha]^{27}_D$ +25.2° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.08 (3 H, s), 0.09 (3 H, s), 0.91 (9 H, s), 1.39 (9 H, s), 1.40 (3 H, s), 1.41 (3 H, s), 1.50 (3 H, s), 3.69 (1 H, dd, *J* = 10.5, 5.2 Hz), 3.79 (1 H, dd, *J* = 10.5, 4.0 Hz), 3.91–4.03 (3 H, m), 4.16 (1 H, dd, *J* = 4.0, 2.1 Hz), 4.27–4.35 (2 H, unresolved); ^{13}C NMR ($CDCl_3$) δ −5.32 (CH_3), −5.23 (CH_3), 18.64 (C), 19.28 (CH_3), 26.09 (CH_3), 26.92 (CH_3), 27.68 (CH_3), 28.69 (CH_3), 43.21 (CH), 64.76 (CH_2), 65.44 (CH_2), 74.03 (CH), 76.94 (CH), 79.52 (CH), 99.64 (C), 106.56 (C); MS *m/z* (relative intensity) 425 ($M^+ + 2 - CH_3$, 6), 423 ($M^+ - CH_3$, 6), 383 (5), 381 (5), 193 (38), 147 (100). Anal. Calcd for $C_{18}H_{35}BrO_5Si$: C, 49.20; H, 8.03. Found: C, 49.33; H, 8.13.

(2*S*,3*R*,4*R*,5*S*)-5-Bromo-2,3:4,6-bis(isopropylidenedioxy)hexan-1-ol (12). To a stirred solution of **11** (1.45 g, 3.3 mmol) in THF (20 mL) was added dropwise a 1.0 M solution of tetrabutylammonium fluoride (10 mL, 10 mmol) in THF at room temperature. After being stirred for 2 h at room temperature, the solution was diluted with $CHCl_3$ (100 mL), washed with water, and dried ($MgSO_4$). Evaporation of the solvent followed by purification by chromatography on silica gel with hexane–ethyl acetate (5:1) afforded **12** (1.05 g, 98%) as colorless crystals: mp 68–70 °C; $[\alpha]^{27}_D$ +21.9 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.42 (3 H, s), 1.44 (3 H, s), 1.51 (3 H, s), 1.98 (1 H, br s), 3.67 (1 H, ddd, *J* = 11.8, 7.0, 4.7 Hz), 3.82 (1 H, dt, *J* = 11.8, 4.7 Hz), 3.85 (1 H, dt, *J* = 9.7, 5.7 Hz), 3.96 (1 H, dd, *J* = 11.8, 9.5 Hz), 4.02 (1 H, dd, *J* = 11.8, 5.7 Hz), 4.14 (1 H, dd, *J* = 9.9, 3.8 Hz), 4.18 (1 H, dd, *J* = 7.3, 3.8 Hz), 4.31 (1 H, dt, *J* = 7.3, 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ 19.27 (CH_3), 26.75 (CH_3), 27.52 (CH_3), 28.65 (CH_3), 43.37 (CH), 63.50 (CH_2), 65.44 (CH_2), 74.05 (CH), 77.52 (CH), 78.25 (CH), 99.75 (C), 109.95 (C); MS *m/z* (relative intensity) 311 ($M^+ + 2-CH_3$, 61), 309 ($M^+ - CH_3$, 62), 193 (41), 131 (35), 85 (47), 59 (100), 43 (100). Anal. Calcd for $C_{12}H_{21}BrO_5$: C, 44.32, H, 6.51. Found: C, 44.34; H, 6.63.

(2*S*,3*S*,4*S*,5*R*)-5-Azido-2,3:4,6-bis(isopropylidenedioxy)hexan-1-ol (13). A mixture of **12** (2.21 g, 6.8 mmol) and sodium azide (2.21 g, 34.0 mmol) in dimethyl sulfoxide (20 mL) was stirred at 120 °C for 4 h. After cooling, water (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with water and dried ($MgSO_4$). The solvent was evaporated to give a brown oil, which was purified by column chromatography on silica gel with hexane–ethyl acetate (5:1) to give **13** (1.25 g, 65%) as a colorless oil: $[\alpha]^{26}_D$ −61.3° (*c* 1.6, $CHCl_3$); IR (neat) 3480, 2110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.42 (3 H, s), 1.43 (3 H, s), 1.49 (3 H, s), 2.32 (1 H, dd, *J* = 7.5, 5.4 Hz), 3.17 (1 H, br s), 3.69–3.79 (2 H, m), 3.91–3.99 (3 H, m), 4.11 (1 H, dd, *J* = 12.8, 1.8 Hz), 4.22 (1 H, dd, *J* = 12.8, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.82 (CH_3), 27.10 (CH_3), 28.56 (CH_3), 54.07 (CH), 63.63 (CH_2), 63.67 (CH_2), 74.02 (CH), 76.13 (CH), 81.51 (CH), 99.59 (C), 109.87 (C); MS *m/z* (relative intensity) 272 ($M^+ - CH_3$, 40), 171 (100), 114 (75); HRMS calcd for $C_{11}H_{18}N_3O_5$ ($M^+ - CH_3$) 272.1246, found 272.1237. Anal. Calcd for $C_{12}H_{21}N_5O_3$: C, 50.16; H, 7.37; N, 14.63. Found: C, 49.52; H, 7.32; N, 14.22.

(2*S*,3*S*,4*S*,5*R*)-5-Amino-2,3:4,6-bis(isopropylidenedioxy)hexan-1-ol (14). A solution of **13** (250 mg, 0.87 mmol) in methanol (8 mL) was hydrogenated over 10% palladium on carbon (200 mg) at atmospheric pressure for 4 h. The mixture was filtered and concentrated in vacuo. The residual oil was chromatographed on silica gel, eluting with ethyl acetate–methanol (10:1) to give **14** (185 mg, 81%) as a colorless oil: $[\alpha]^{25}_D$ +7.61° (*c* 0.7, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (6 H, s), 1.37 (3 H, s), 1.42 (3 H, s), 2.13 (3 H, br m), 2.76 (1 H, d, *J* = 2.2 Hz), 3.67 (1 H, d, *J* = 1.8 Hz), 3.68 (1 H, d, *J* = 0.8 Hz), 3.71 (1 H, d, *J* = 1.8 Hz), 3.85–3.76 (2 H, unresolved), 3.96 (1 H, ddd, *J* = 8.7, 5.1, 2.2 Hz), 4.09 (1 H, dd, *J* = 11.9, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.80 (CH_3), 27.01 (CH_3), 27.11 (CH_3), 29.39 (CH_3), 45.76 (CH), 63.57 (CH_2), 66.98 (CH_2), 74.31 (CH), 76.66 (CH), 81.04 (CH), 99.07 (C), 109.38 (C); CIMS (isobutane) *m/z* (relative intensity) 262 (M^+ + 1, 19), 246 (28), 188 (23), 172 (36), 114 (32), 100 (58), 72 (100).

(2*S*,3*S*,4*S*,5*R*)-2,3:4,6-Bis(isopropylidenedioxy)-5-[[[(*p*-methoxybenzyl)oxy]carbonyl]amino]hexan-1-ol (15). To a solution of **14** (399 mg, 1.53 mmol) and triethylamine (170 mg, 1.68 mmol) in dioxane (4 mL) was added a solution of *p*-methoxybenzyl *S*-4,6-dimethylpyrimidin-2-yl thiocarbonate (688 mg, 1.68 mmol) in dioxane (2 mL). After the solution was stirred at room temperature for 4 h, it was diluted with CH_2Cl_2 (50 mL), washed with water, and dried over $MgSO_4$. Evaporation of the solvent left an oil, which was chromatographed on silica gel with hexane–ethyl acetate (10:1) to give **15** (607 mg, 93%) as a colorless oil: $[\alpha]^{25}_D$ −32.7° (*c* 1.3, $CHCl_3$); IR (neat) 3610, 3450, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 1.35 (3 H, s), 1.37 (3 H, s), 1.45 (3 H, s), 2.34 (1 H, br s), 3.60–3.95 (total 10 H, m, containing 3 H, s at 3.79 ppm), 4.05 (1 H, d, *J* = 11.7 Hz), 5.02 (1 H, d, *J* = 11.7 Hz), 5.07 (1 H, d, *J* = 10.7 Hz), 5.50 (1 H, d, *J* = 7.9 Hz), 6.88 (2 H, d, *J* = 8.5 Hz), 7.32 (1 H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.74 (CH_3), 27.00 (CH_3), 29.42 (CH_3), 45.62 (CH), 55.38 (CH_3), 63.40 (CH_2), 65.00 (CH_2), 66.85 (CH_2), 73.84 (CH), 75.37 (CH), 81.04 (CH), 99.53 (C), 109.73 (C), 114.10 (CH), 128.69 (C), 130.11 (CH), 156.05 (C), 159.79 (C); MS *m/z* (relative intensity) 425 (M^+, 0.8), 138 (20), 137 (20), 131 (25), 121 (10); HRMS calcd for $C_{21}H_{31}NO_8$ (M^+) 425.2050, found 425.2066.

(2*R*,3*S*,4*S*,5*R*)-2,3:4,6-Bis(isopropylidenedioxy)-5-[[[(*p*-methoxybenzyl)oxy]carbonyl]amino]hexanal (16). To a stirred, cooled (−78 °C) solution of oxalyl chloride (479 mg, 3.74 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of dimethyl sulfoxide (658 mg, 7.47 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for 30 min. To this mixture was added dropwise a solution of **15** (765 mg, 180 mmol) in CH_2Cl_2 (3 mL) over 5 min, and stirring was continued at −78 °C. After 1 h, triethylamine (1.13 g, 11.2 mmol) was added to the reaction mixture, and the mixture was stirred for 30 min and then allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography with hexane–ethyl acetate (1:1) to afford **16** (746 mg, 98%) as a pale yellow oil: $[\alpha]^{25}_D$ −25.0° (*c* 1.3, $CHCl_3$); IR (neat) 3400, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32–1.45 (12 H, m), 3.43–4.11 (total 9 H, m, containing 3 H, s at 3.77 ppm), 4.99–5.09 (2 H, m), 5.51 (1 H, d, *J* = 8.9 Hz), 6.86 (2 H, d, *J* = 8.4 Hz), 7.30 (2 H, d, *J* = 8.4 Hz); MS *m/z* (relative intensity) 423 (M^+, 1), 365 (14), 228 (19), 138 (77), 121 (100); HRMS calcd for $C_{21}H_{29}NO_8$ (M^+) 423.1893, found 423.1896.

(+)-Galactostatin-1-sulfonic Acid (17). A stirred, ice-cold suspension of **16** (255 mg, 0.60 mmol) in water (2 mL) was saturated with SO_2 to give a homogeneous solution, which was allowed to stand at room temperature for 60 h. The reaction mixture was diluted with methanol (1 mL), cooled to 0 °C, and saturated again with SO_2. The mixture was allowed to stand at cooling to generate a white solid, which was collected by filtration, washed

(25) The disagreement between observed and reported melting points is probably due to the considerably hygroscopic character of **17**, which sometimes resulted in a lowering of the melting point.

with methanol–ether (1:1), and dried in vacuo to give colorless needles of **17** (69 mg, 47%): mp 146–150 °C dec (lit.[12b] mp 133–135 °C);[25] $[\alpha]^{25}_D$ +19.6° (*c* 0.9, H_2O) [lit.[12b] $[\alpha]^{23}_D$ +17.2° (*c* 0.5, H_2O)]; ^1H NMR (D_2O) δ DOH (4.70) 3.40 (1 H, br t, *J* = 6.7 Hz), 3.66 (1 H, dd, *J* = 9.5, 3.2 Hz), 3.82 (2 H, d, *J* = 6.7 Hz), 4.00 (1 H, d, *J* = 10.3 Hz), 4.62 (2 H, unresolved); ^{13}C NMR [D_2O with $Me_3Si(CH_2)_3SO_3Na$ as internal standard] δ 61.40, 62.77, 68.87, 69.15, 73.26, 75.39; MS *m/z* (relative intensity) 143 (M^+ – 100, 19), 112 (41), 102 (49), 84 (45), 64 (100).

(+)-Galactostatin (5). A solution of **17** (69 mg, 0.284 mmol) in water (1 mL) was passed through a column of Dowex 1-X8 (OH^-) resin (100–200 mesh) and eluted with water. The eluent was concentrated in vacuo below 40 °C, and the residue was precipitated by adding ethanol to give a colorless amorphous powder of **5** (35 mg, 69%): mp 93–95 °C dec (lit.[12b] mp 94–98 °C); $[\alpha]^{25}_D$ +84.6° (*c* 0.3, H_2O) [lit.[12b] $[\alpha]^{23}_D$ +85.6 ● 1.2° (*c* 1.0, H_2O)].

^1H and ^{13}C NMR spectra of synthetic **5** were superimposable with those of natural **5**.

(2*S*,3*S*,4*S*,5*R*)-5-[(Benzyloxycarbonyl)amino]-2,3:4,6-bis(isopropylidenedioxy)hexan-1-ol (18). To a solution of **14** (1.03 g, 4.13 mmol) in CH_2Cl_2 (10 mL) was added a solution of Na_2CO_3 (482 mg, 4.55 mmol) in water (10 mL), and the mixture was cooled in an ice bath. To this solution was added dropwise a solution of benzyl chloroformate (0.77 g, 4.51 mmol) in CH_2Cl_2 (10 mL) with stirring, and the mixture was stirred at room temperature for 3 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexane–ethyl acetate (3:1) to give **18** (1.59 g, 97%) as a colorless oil: $[\alpha]^{25}_D$ –43.5° (*c* 0.6, $CHCl_3$); IR (neat) 3450, 3310, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s), 1.37 (3 H, s), 1.39 (3 H, s), 1.47 (3 H, s), 2.30 (1 H, br dd, *J* = 6.4, 5.6 Hz), 3.61–3.92 (6 H, unresolved), 3.95 (1 H, dd, *J* = 8.6, 1.7 Hz), 4.09 (1 H, dd, *J* = 12.0, 1.3 Hz), 5.09 (1 H, d, *J* = 12.2 Hz), 5.13 (1 H, d, *J* = 12.2 Hz), 5.53 (1 H, d, *J* = 9.7 Hz), 7.30–7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 18.72 (CH_3), 26.93 (CH_3), 27.07 (CH_3), 29.39 (CH_3) 45.76 (CH), 63.31 (CH_2), 64.85 (CH_2), 67.03 (CH_2), 75.23 (CH), 75.53 (CH), 80.99 (CH), 99.53 (C), 109.90 (C), 128.30 (CH, 3 carbons), 128.63 (CH, 2 carbons), 136.48 (C) 155.90 (C); CIMS (isobutane) *m/z* (relative intensity) 396 (M^+ + 1, 44), 380 (20), 338 (100), 306 (11), 177 (15); HRMS calcd for $C_{20}H_{29}NO_7$ (M^+) 395.1944, found 395.1967.

(2*S*,3*S*,4*S*,5*R*)-5-[(Benzyloxycarbonyl)amino]-2,3:4,6-bis(isopropylidenedioxy)-1-[(methylsulfonyl)oxy]hexane (19). To a cold (0 °C) solution of **18** (188 mg, 0.475 mmol) and triethylamine (73 mg, 0.721 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of methanesulfonyl chloride (82 mg, 0.716 mmol) in CH_2Cl_2 (5 mL). After the mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h, it was diluted with CH_2Cl_2 (50 mL), washed with water, and dried ($MgSO_4$). Evaporation of the solvent afforded an oily residue, which was chromatographed on silica gel eluting with hexane–ethyl acetate (2:1) to give **19** (217 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ +40.7° (*c* 0.1, $CHCl_3$); IR (neat) 3390, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 1.46 (3 H, s), 3.03 (3 H, s), 3.74 (1 H, t, *J* = 8.3 Hz), 3.81 (1 H, d, *J* = 12.3 Hz), 3.89 (1 H, dd, *J* = 9.8, 1.1 Hz), 3.95 (1 H, d, *J* = 8.3 Hz), 4.05 (1 H, s), 4.07–4.09 (1 H, unresolved), 4.16 (1 H, dd, *J* = 11.2, 6.5 Hz), 4.45 (1 H, dd, *J* = 11.2, 1.8 Hz), 5.09 (1 H, d, *J* = 12.0 Hz), 5.19 (1 H, d, *J* = 12.0 Hz), 5.51 (1 H, d, *J* = 9.8 Hz), 7.32–7.40 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 18.66 (CH_3), 26.64 (CH_3), 27.13 (CH_3), 29.36 (CH_3), 37.78 (CH_3), 45.72 (CH), 64.06 (CH_2), 67.75 (CH_2), 70.02 (CH_2), 73.65 (CH), 73.80 (CH), 78.57 (CH), 99.49 (C), 110.82 (C), 128.29 (CH, 3 carbons), 128.62 (CH, 2 carbons), 136.46 (C), 155.98 (C); CIMS (isobutane) *m/z* (relative intensity) 474 (M^+ + 1, 6), 459 (5), 458 (48), 415 (39), 384 (86), 294 (23), 177 (100), 132 (94); HRMS calcd for $C_{20}H_{29}NO_9S$ (M^+ – CH_3) 459.1563, found 459.1591.

2,3:4,6-*O*-Di(isopropylidene)-1,5-deoxy-1,5-imino-D-galactitol (20). A solution of **19** (103 mg, 0.217 mmol) in methanol (2 mL) was hydrogenated over 10% palladium on carbon (100 mg) at atmospheric pressure for 3.5 h. After filtration, triethylamine (110 mg, 1.09 mmol) was added to the filtrate and the solution was refluxed for 4.5 h. Evaporation in vacuo and silica gel chromatography with $CHCl_3$–methanol (9:1) gave a colorless solid of **20** (30 mg, 57%): mp 69–70 °C; $[\alpha]^{27}_D$ +80.4° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (3 H, s), 1.42 (3 H, s), 1.45 (3 H, s), 1.48 (3 H, s), 1.96 (1 H, br s), 2.40 (1 H, m), 2.69 (1 H, dd, *J* = 12.6, 4.4 Hz), 3.36 (1 H, dd, *J* = 9.2, 2.6 Hz), 3.39 (1 H, dd, *J* = 12.6, 10.8 Hz), 3.81 (1 H, dd, *J* = 12.2, 1.4 Hz), 3.89 (1 H, ddd, *J* = 10.8, 9.2, 4.4 Hz), 4.17 (1 H, dd, *J* = 12.2, 2.6 Hz), 4.48 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 18.44 (CH_3), 26.61 (CH_3), 26.66 (CH_3), 29.62 (CH_3), 47.78 (CH_2), 51.00 (CH_2), 64.41 (CH), 68.61 (CH), 71.16 (CH), 81.39 (CH), 98.91 (C), 109.24 (C); MS *m/z* (relative intensity) 243 (M^+, 7), 185 (53), 170 (25), 147 (29), 128 (25), 127 (25), 113 (41), 98 (100), 69 (63); HRMS calcd for $C_{12}H_{21}NO_4(M^+)$ 243.1471, found 243.1454.

(+)-1-Deoxygalactostatin (6). To a solution of **20** (29 mg, 0.119 mmol) in methanol (1 mL) was added concentrated HCl (0.5 mL), and the mixture was refluxed for 4.5 h. The mixture was concentrated in vacuo, and the residue was purified by using ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh) eluting with water. Subsequent evaporation of water in vacuo below 40 °C afforded a colorless syrup, which was dissolved in a small amount of methanol and then precipitated by addition of acetone to give a hygroscopic, amorphous solid of **6** (17 mg, 87%): $[\alpha]^{28}_D$ +52.6° (*c* 1.3, H_2O) [lit.[13] $[\alpha]^{23}_D$ +52.8° (*c* 1.0, H_2O)]; ^1H NMR (D_2O) δ DOH 2.56 (1 H, dd, *J* = 12.6, 10.8 Hz), 2.92 (1 H, dd, *J* = 6.6, 1.3 Hz), 3.31 (1 H, dd, *J* = 12.6, 10.8 Hz),3.65 (1 H, dd, *J* = 9.7, 3.1 Hz), 3.78 (1 H, dd, *J* = 10.8, 6.6 Hz), 3.83 (1 H, dd, *J* = 10.8, 6.6 Hz), 3.93 (1 H, ddd, *J* = 10.8, 9.7, 5.3 Hz), 4.18 (1 H, dd, *J* = 3.1, 1.3 Hz); ^{13}C NMR (D_2O with acetonitrile as internal standard) δ 49.89, 59.67, 62.25, 69.02, 70.11, 75.91.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **10**, **14–16**, and **18–20** reported in the experimental section (13 pages). Ordering information is given on any current masthead page.