SYNTHESIS OF (+)-GALACTOSTATIN[1]

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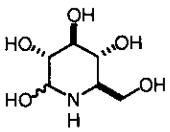
Abstract—The chiral synthesis of (+)-galactostatin (**3**), a new ß-galactosidase inhibitor, has been achieved, in which the key step involved a diastereoselective epoxidation of the allylic alcohol (**4**) derived from L-tartaric acid.

Nojirimycin (1)[2] and nojirimycin B (mannojirimycin) (2)[3] are the first members of 5-deoxy-5-iminohexitols encountered in nature, i.e., analogs of pyranose sugars in which the ring oxygen is replaced by nitrogen. They have been shown to be potential specific inhibitors of the hydrolysis of the corresponding glycopyranosides (D-gluco- and D-mannopyranosides) by the specific glycosidases. Very recently, galactostatin (3), the corresponding analog of D-galactose, has been first isolated from Streptomyces lydicus PA-5726[4] and has been found to display strong inhibitory activity toward several ß-galactosidases.[4a,5] In this communication, we wish to report the first total synthesis of naturally occurring (+)-galactostatin (3) starting from L-tartaric acid.



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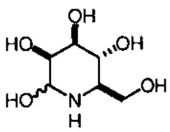

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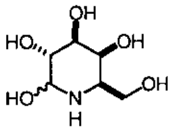


3

The required starting allylic alcohol **4** was easily derived from L-tartaric acid according to the process worked out previously in this laboratory.[6] Epoxidation of **4** was performed by using various peracids and tert-butyl hydroperoxide—vanadyl acetylacetonate. The results are presented in Table 1. In all cases, the

Scheme 1

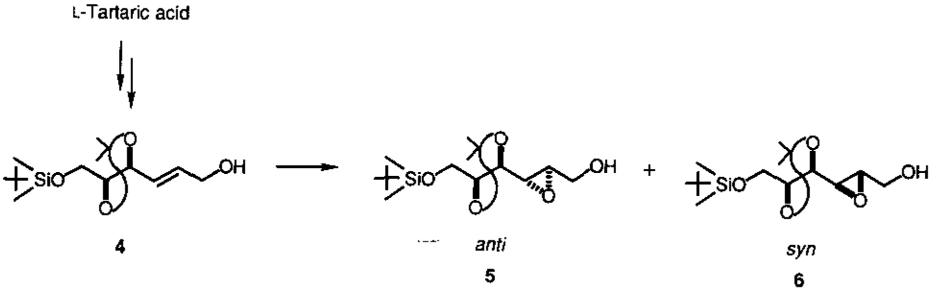


Table 1. Stereoselectivity in the Epoxidation of Allylic Alcohol 4

entry	oxidant[a)]	temp, °C	syn/anti ratio[b)]	yield, %
1	m-$ClC_6H_4CO_3H$	0	35:65	95
2	m-$ClC_6H_4CO_3H$	-20	30:70	88
3	CH_3CO_3H	r.t.	29:71	81
4	CF_3CO_3H	r.t.	12:88	41
5	t-BuO_2H/VO(acac)$_2$	100	32:68	50

a) The reaction was carried out in a CH_2Cl_2 (entries 1–4) or a benzene solution (entry 5). b) Determined by 400-MHz ^1H nmr integration.

reaction showed an appreciable anti diastereomeric bias leading to 5, though in the case of trans-allylic alcohols without the alkyl substituent at the C_2 position the degree of the stereoselectivity has been reported to be low[7] or not to be observed.[8] The anti selectivity observed with peracids (Table 1, entries

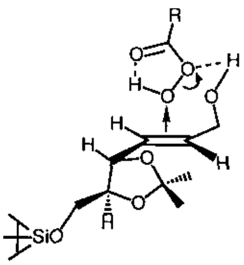
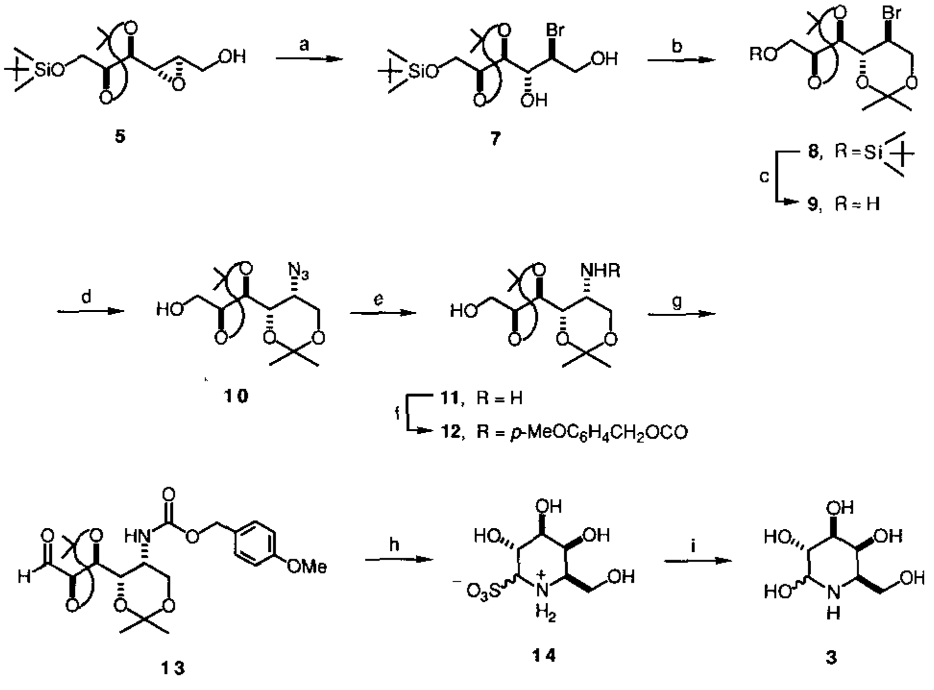


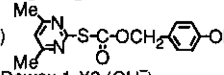
Figure 1

1–4) would be predicted by the transition state model depicted in Figure 1 where the conformation with the α-alkoxy group inside and the alkyl group anti is stabilized due to inside alkoxy effect,[9] in which the developing bond forms trans to the alkyl group to permit an anti periplanar approach, thus leading to the anti selectivity. A similar picture involving the inside alkoxy transition state seems to be drawn for the rationale to interpret the anti stereodifferentiation observed in the vanadium catalyzed epoxidation with tert-butyl hydroperoxide[10] (Table 1, entry 5).

The anti epoxide 5 thus obtained was elaborated to (+)-galactostatin (3) as outlined in Scheme 2. Regio- and stereoselective epoxide-opening reaction of 5 was carried out with Li_2NiBr_4[11] (THF, 80 °C) to give the bromohydrin 7 in 74% yield, which was converted to the diacetonide 8, $[\alpha]^{27}_D$ +25.2° (c 2.0, $CHCl_3$), with acetone dimethyl acetal (acetone, TsOH, reflux). Desilylation (n-Bu_4NF, THF) of 8 led to the alcohol 9, $[\alpha]^{27}_D$ -21.9° (c 1.1, $CHCl_3$), in 98% yield.

Scheme 2



(a) Li_2NiBr_4, THF, 80 °C; (b) $(MeO)_2CMe_2$, TsOH, acetone; (c) $(n\text{-}Bu)_4NF$, THF; (d) NaN_3, Me_2SO; (e) H_2, Pd–C, MeOH; (f)  , Et_3N, dioxane; (g) $(COCl)_2$, Me_2SO, Et_3N; (h) SO_2, H_2O; (i) Dowex 1-X8 (OH^-).

Nucleophilic displacement of **9** was performed by NaN_3 in Me_2SO to afford the azide **10**, $[\alpha]^{26}_{D}$ -61.3° (*c* 1.6, $CHCl_3$), in 64% yield. After catalytic hydogenation (82% yield), the resulting amine 11, $[\alpha]^{25}_{D}$ +7.6° (*c* 0.7, $CHCl_3$), was subjected to selective N-protection by treatment with *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate[12] to give the carbamate 12, $[\alpha]^{25}_{D}$ -32.7° (*c* 1.3, $CHCl_3$), in 93% yield. Swern oxidation [$(COCl)_2$, Me_2SO, Et_3N] of 12 afforded the aldehyde 13, $[\alpha]^{25}_{D}$ -25.0° (*c* 1.3, $CHCl_3$), in 98% yield. Upon exposure to aqueous sulfurous acid at room temperature, 13 smoothly underwent deprotection to yield 1-deoxygalactostatin-1-sulfonic acid (bisulfite adduct) (**14**), mp 146–150 °C dec; $[\alpha]^{25}_{D}$ +19.6° (*c* 0.5, H_2O) [lit.[4b] mp 133–135 °C; $[\alpha]^{23}_{D}$ +17.2° (*c* 0.5, H_2O)], in 47% yield, whose spectral characteristics were identical to those for naturally derived material. Finally, **14** was applied to a column of ion exchange resin [Dowex 1-X8 (OH^-)] and eluted with water to furnish (+)-galactostatin (3), mp 93–95 °C dec; $[\alpha]^{25}_{D}$ +84.6° (*c* 0.13, H_2O) [lit.[4a] mp 94–98 °C; $[\alpha]^{23}_{D}$ +85.6±1.2° (*c* 1.0, H_2O)], in 69% yield. Synthetic 3 had identical spectra (^{1}H and ^{13}C nmr and mass) with the corresponding authentic spectra of natural 3.

ACKNOWLEDGMENT

We are indebted to Dr. Y. Miyake of Shionogi Research Laboratories for generous providing of samples of natural (+)-galactostatin and its bisulfite adduct.

REFERENCES AND NOTES

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Received, 29th September, 1989