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Amino and Hydroxy Acid Based Diastereoselective Synthesis of 1-Deoxygalactostatin and its Imino Acid Derivative

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Abstract: 1-Deoxygalactostatin (**2**) and (2*S*, 3*S*, 4*R*, 5*S*)-trihydroxypipecolic acid (**15**) have been synthesised from known building blocks derived from glycine, D-valine and L-tartaric acid (eight and seven steps, with 23% and 27% yield, respectively), *via* a *syn*-aldol reaction between 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose (**6**) and the stannous salt of the Schöllkopf's bislactim ether **7b**. © 1999 Elsevier Science Ltd. All rights reserved.

Polyhydroxylated alkaloids, commonly named as aza sugars, are interesting candidates for the competitive inhibition of glycoconjugate processing enzymes.[1] When protonated, polyhydroxylated piperidines resemble the transient oxocarbonium ion involved in glycoside hydrolysis, and thus can act as transition-state analogues for the inhibition of the glycosidases of the sugars they mimic. In particular, galactostatin (**1**, see Figure 1), isolated from the culture broth of *Streptomyces lydicus* PA5726,[2] and its reduced product, 1-deoxygalactostatin (**2**, 1,5-dideoxy-1,5-imino-D-galactitol) are potent and specific inhibitors of several α- and β-D-galactosidases.[3] 1-Deoxygalactostatin also functions as an affinity ligand for the purification of galactosidases,[4] while its *N*-alkylated analogues were also found to inhibit glycosphingolipid biosynthesis.[5] Because of their utility in theoretical studies of glycosidase function [6] and their potential for the treatment of several clinical conditions,[7] as well as because of their challenging structures, compounds **1** and **2** have attracted extensive synthetic efforts. Nevertheless, in spite of the numerous synthesis of 1-deoxygalactostatin which have appeared, only three non-carbohydrate-based routes are currently available.[8,9]

Figure 1

galactostatin (**1**)   1-deoxygalactostatin (**2**)

In this paper we wish to describe a new non-carbohydrate-based approach to **2**, utilising as key feature an adaptation of our amino acid-based diastereoselective synthesis of 2-amino-2-deoxyhexoses.[10] The implementation of this strategy to the synthesis of 1-deoxygalactostatin depended on the cyclization of the amino acid **3** (see Scheme 1), *via* nucleophilic substitution of an activated hydroxyl group, followed by the reduction of the carboxylic acid group. We envisaged preparing key intermediate **3** from a 4-carbon building block and a

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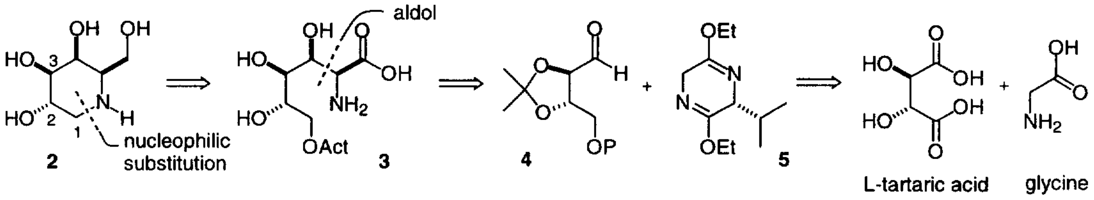
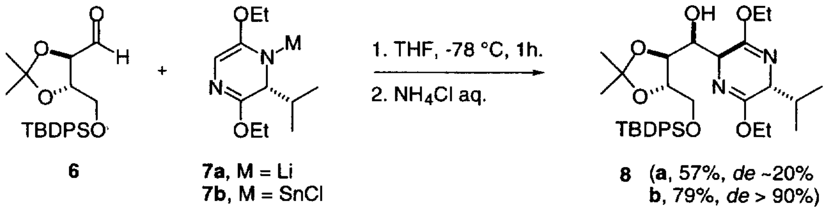
chiral glycine equivalent by a stereocontrolled aldol addition. Aldehyde **4**, derived from L-tartaric acid, was sought as an appropriate precursor, delivering the required configuration at positions 2 and 3 and being suitably functionalized at position 1. Moreover, addition of organometallics to 2,3-isopropylidene-L-threose derivatives, like **4**, generally proceed with *anti* selectivity.[11] On the other hand, we found Schöllkopf's bislactim ethers (like **5**)[12] to be very attractive, due to the high *syn* selectivity shown by these reagents in aldol-type reactions.[13] As the aldehyde and the azaenolate derived from **5** form a matched pair, a double asymmetric induction of the desired 3,4-*anti*-4,5-*syn* configuration should take place in the key step.

Scheme 1



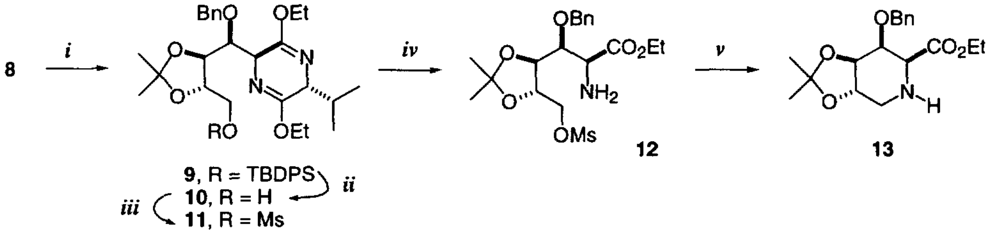
According to the literature, L-tartaric acid was converted into 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose (**6**, see Scheme 2),[14] while (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine (**5**) was prepared from glycine and D-valine.[15] We have previously succeeded in the construction of a *syn,anti* aminodiol fragment by using the aldol reaction between lithiated Schöllkopf's bislactim ether and 1,3-dioxolane- or furanoside-4-carboxaldehyde derivatives.[10,16] Thus, for the synthesis of 1-deoxygalactostatin, the addition of the more accessible but usually less selective lithium azaenolate **7a**[13,17] to the aldehyde **6** was first examined. Reaction of **6** with 1.2 equivalents of lithium salt **7a** in tetrahydrofuran at -78 °C afforded, after quenching, aqueous work-up and removal of the excess of **5**,[18] a crude mixture containing adduct **8** along with two other minor isomers, in a 3:1:1 ratio[19] and 57% combined yield. The separation of the components of this mixture could be achieved by flash chromatography (using SiO_2 and AcOEt/hexane as eluent), to provide **8** with high purity (*de* > 98%) on a multigram scale.[20] However, the selective formation of the major isomer could be increased by using a tin(II) azaenolate **7b**, as was recently described by Kobayashi *et al.*[22] Thus, when the lithium azaenolate **7a** was allowed to react in tetrahydrofuran at low temperature with an equimolar amount of stannous chloride for one hour prior to the addition of the aldehyde, the mixture of adducts was obtained in 79% of yield, containing **8** with a diastereomeric excess of 90%.[23]

Scheme 2



Conversion of adduct **8** to the target aza sugar required, in addition to the removal of the chiral auxiliary and reduction of the carboxylic acid group, the selective activation of the primary hydroxy group for the cyclization step. In order to avoid competitive ring closure processes to furan derivatives, previous orthogonal protection of the secondary hydroxy group was deemed. Treatment of adduct **8** with sodium hydride and benzyl bromide in the presence of a catalytic amount of tetrabutylammonium iodide led to the benzyl ether **9** in good yield. After deprotection of the silyl ether the mesylation of the alcohol **10** was accomplished in almost quantitative yield. Selective hydrolysis of the pyrazino moiety of **11**, in the presence of the isopropylidene ketal, took place without cyclization and yielded the amino ester **12** in good yield, after removal of the auxiliary valine by flash chromatography. Although the amino ester underwent a slow conversion to piperidine **13** on standing, cyclization was completed by heating **12** in dimethylsulfoxide with triethylamine as an auxiliary base.

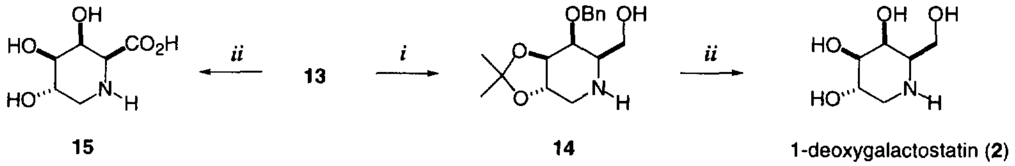
Scheme 3



Reagents and conditions: *i.* NaH, BnBr, NBu_4I, 24h, rt, 75%. *ii.* NBu_4F, THF, rt, 4h, 95%. *iii.* MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 1h, 100%. *iv.* 0.25M HCl:EtOH 1:2, 9h, 65%. *v.* DMSO, Et_3N, 70°C, 2h, 85%.

Reduction of the piperidine ester **13** with lithium triethylborohydride proceeded cleanly (see Scheme 4), as previously described for other piperidine derivatives with acidic functionality.[24] Finally, deprotection of **14** by catalytic hydrogenation in acidic media (THF:HCl 0.25N 1:1) allowed, after purification by ion-exchange chromatography (Dowex 50x8-200, H^+) and reverse phase flash chromatography (H_2O, RP-18 230-400 mesh), the isolation of the free 1-deoxygalactostatin in high yield.[25] Imino acid **15**, an analogue of galacturonic acid which has shown a potent inhibition of several α-galactosidases and galacturonases,[26] is also readily available from the piperidine ester **13**. Thus, under the conditions employed for deprotection of the alcohol **14**, the intermediate **13** gave rise to the pipecolic acid **15**, that could be isolated in excellent yield after ion-exchange and reverse phase flash chromatography.[27]

Scheme 4



Reagents and conditions:
i. $LiEt_3BH$, THF, rt, 2h, 84%. *ii.* a. 0.25M HCl/THF 1:1, H_2, Pd/C, rt, 9h. b. Dowex-H^+, 90% of **2** and 88% of **15**.

The successful synthesis of 1-deoxygalactostatin and (2*S*, 3*S*, 4*R*, 5*S*)-trihydroxypipecolic acid demonstrates the efficacy of strategies employing a chiral glycine equivalent in the asymmetric synthesis of polyhydroxylated alkaloids. Further applications of this methodology to the synthesis of other imino sugars and imino acids with biological activity are in progress.

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15. (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine was prepared by treatment of *cyclo*[(2*R*)-val-gly] with triethyloxonium tetrafluoroborate. See Rose, J.E., Leeson, P.D.; Gani, D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 157. Alternatively, both enantiomers of the related 2,5-dimethoxy-3-isopropyl-3,6-dihydropyrazine can be purchased from E. Merck.
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18. The excess of Schöllkopf's reagent could be recovered, and showed no racemization.
19. The diastereoselectivity was determined by integrating of the pairs of doublets corresponding to the isopropyl groups in the ^{1}H NMR spectrum of the mixture of adducts.
20. All new compounds have been isolated in a pure analytical form after chromatography (on SiO_2 or RP-18), and their spectral data (FABMS, NMR and IR) were consistent with the proposed structure. Selected data for compound **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.77 (d, 3H, J = 6.8 Hz); 1.04 (d, 3H, J = 6.8 Hz); 1.05 (s, 9H); 1.23 (t, 3H, J = 7.3 Hz); 1.31 (t, 3H, J = 7.3 Hz); 1.45 (s, 6H); 2.02 (d, 1H, J = 9.3 Hz); 2.25 (dsep, 1H, J = 3.4, 6.8 Hz); 3.84 (d, 2H, J = 4.4 Hz); 3.98 (t, 1H, J = 3.4 Hz); 4.01-4.28 (m, 7H); 4.40 (dd, 1H, J = 6.4, 8.8 Hz); 7.33-7.44 (m, 6H); 7.65-7.75 (m, 4H). $[\alpha]^{20}_D$ = - 8.5 (c = 2.0, CH_2Cl_2).
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25. Optical rotation for **2**·HCl: $[\alpha]^{24}_D$ = +44.6 (c = 0.9, H_2O) [ref 8e: $[\alpha]^{25}_D$ = +41.7 (c = 0.3, H_2O)]. ^{1}H NMR, ^{13}C NMR and FABMS spectral data obtained for this material were also in accordance with the literature values (see references 8 and 9).
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27. Selected data for **15**·HCl (no data available in the literature): ^{1}H NMR (200 MHz, D_2O) δ: 2.55 (dd, J = 12.5, 11.4 Hz, H1ax); 3.17 (dd, J = 12.5, 5.3 Hz, H1eq); 3.36 (dd, J = 9.7, 3.0 Hz, H3); 3.69 (ddd, J = 11.4, 9.7, 5.3 Hz, H2); 3.94 (d, J = 1.8 Hz, H5); 4.20 (dd, J = 3.0, 1.8 Hz, H4). ^{13}C NMR (200 MHz, D_2O) δ: 45.98 (CH_2), 61.03 (CH), 64.91 (CH), 68.69 (CH), 73.28 (CH), 169.65. $[\alpha]^{26}_D$ = +20.3 (c = 1.3, H_2O).