Pergamon

Tetrahedron Letters 43 (2002) 4653–4655

TETRAHEDRON LETTERS

Glycal-mediated syntheses of enantiomerically pure polyhydroxylated γ- and δ-lactams

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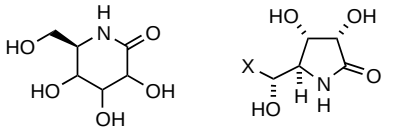
Received 22 March 2002; revised 2 May 2002; accepted 3 May 2002

Abstract—Syntheses of new enantiomerically pure γ-lactams **4a**,**b** and δ-lactams **5a**,**b** from D-glucal (**3a**) and D-galactal (**3b**) as starting materials are described.

Azasugars, structurally related to cyclic carbohydrates in which the ring oxygen is replaced by a nitrogen atom, and analogues compounds are potent and selective glycosidase inhibitors, and thus they have potential chemotherapeutic applications in the prevention and treatment of diseases such as cancer, diabetes and AIDS.[1]

These considerations have stimulated over the last decades a vigorous activity for the syntheses of such compounds, and excellent studies on the relationship between their structures and inhibitory properties have been reported.[2,3] Since the hemiaminal moiety in azasugars is reported to undergo easy dehydration, and the lack of hydroxyl at C-2 to lower inhibition,[3,4] recent work showed that more stable δ-lactams can act as nonbasic glycosidase inhibitors.[5] The syntheses of all eight stereoisomers of D-glyconic-δ-lactams **1**[6] and γ-lactams **2** (Fig. 1) have been accomplished mainly from carbohydrates or other naturally occurring compounds,[7] and their glycosidase inhibitory properties have been evaluated.



1 **2a:** X = CH_2OH **2b:** X = H

Figure 1.

Glycals (1,5-anhydro-hex-1-enitols) are important building blocks in the oligosaccharide chemistry,[8] and only very recently have they been employed via imino-glycals in the synthesis of polyhydroxylated piperidines and dihydropyridones.[9]

Herein we report a new synthetic strategy to the unknown enantiomerically pure γ-lactams **4** and δ-lactams **5** from D-glucal (**3a**) and D-galactal (**3b**) (Scheme 1).

Starting material for the synthesis of γ-lactams **4** were, respectively, D-glucal (**3a**) and D-galactal (**3b**), which were converted in an optimized one-pot procedure via selective 3,6-di-*O*-benzoylation[10] into the mesylates **6** (Scheme 2). Subsequent treatment with sodium azide/tetrabutylammonium chloride in toluene gave the corresponding azides **7**. A two-step hydration oxidation sequence with pyridinium chlorochromate (PCC) in dichloromethane was required to yield lactones **8**. The direct oxidation of **7**, although an efficient procedure for analogues substrates,[11] gave unsatisfactory results. Hydrogenation in the presence of palladium on carbon yielded the protected γ-lactams **9**, which were quantitatively debenzoylated with sodium methanolate in methanol to give the target compounds **4**.[12]

The syntheses of the epimeric δ-lactams **5a** and **5b** obtained from D-glucal (**3a**) and D-galactal (**3b**), respectively, are summarized in Scheme 3. Tri-*O*-benzyl-D-glucal (**10a**) and tri-*O*-benzyl-D-galactal (**10b**), easily prepared by total protection of the starting glycals, were converted into lactones **11** by direct oxidation with PCC in 1,2-dichloroethane at reflux. Transesterifi-

Keywords: lactams; azasugars; glycals; carbohydrates.

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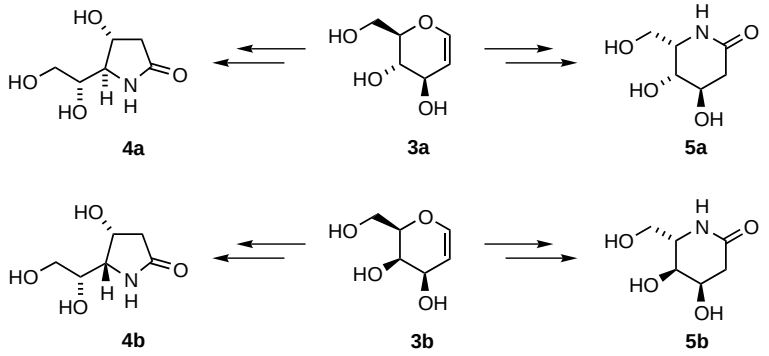
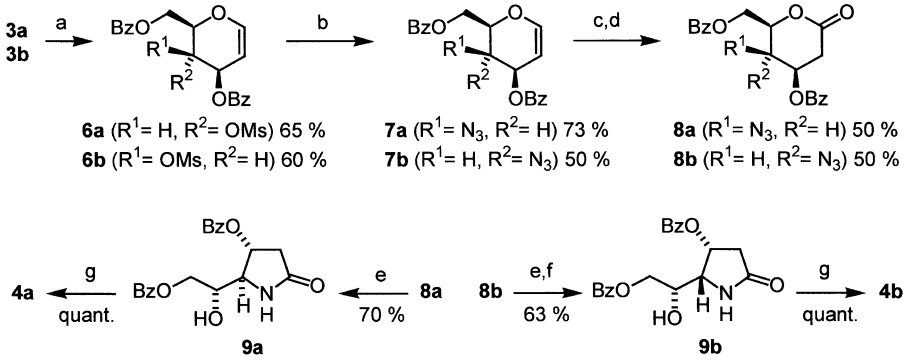
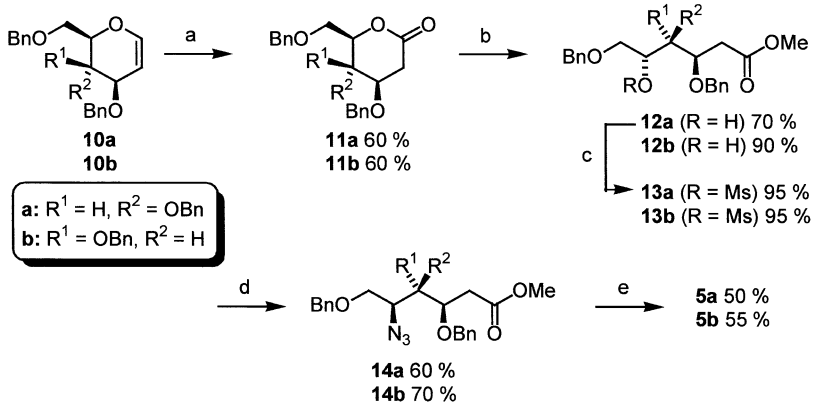
PII: S0040-4039(02)00852-3



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) 2.3 equiv. BzCl, pyridine, 0°C, 1.5 h, then 2 equiv. MsCl, 0°C→rt, 0.5 h; (b) 3.5 equiv. NaN_3, 3 equiv. Bu_4NCl, toluene, reflux, 24 h; (c) 30 equiv. HCl (12 M), dioxane, rt, 12 h; (d) PCC, CH_2Cl_2, rt, 48 h; (e) H_2, Pd/C, AcOEt, rt, 2 h; (f) *p*-TsOH cat., benzene, reflux, 1 h; (g) NaOMe, MeOH, rt, 0.5 h.



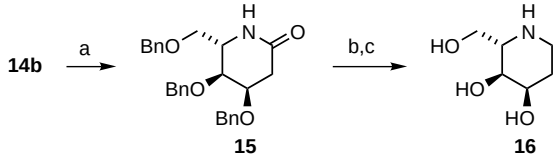
Scheme 3. *Reagents and conditions*: (a) 2.2 equiv. PCC, 1,2-dichloroethane, reflux, 6 h; (b) MeOH, H_2SO_4 cat., reflux, 6 h; (c) 2 equiv. MsCl, pyridine, 0°C→rt, 6 h; (d) 10 equiv. NaN_3, DMF, reflux, 24 h; (e) H_2, Pd/C, EtOH/MeOH (3:1), rt, 24 h.

cation with $MeOH/H_2SO_4$ cat. led to the open chain hydroxy methyl esters **12** which, after mesylation to **13**, underwent S_N2 substitution with sodium azide in DMF at reflux to give the azides **14**. Finally, hydrogenation with palladium on carbon as catalyst in EtOH/MeOH provided the target molecules **5a** and **5b** in one step.[13]

To demonstrate the utility of our synthetic strategy, we report an example of further synthetic application toward highly functionalized piperidines.

Reductive hydrogenation on **14b** in AcOEt as solvent afforded the totally protected δ-lactam **15**, which, after treatment with lithium aluminiumhydride and subsequent debenzylation, yielded fagomine[14] isomer **16**[15] (Scheme 4). The yields for this reaction sequence were not optimized.

In summary, we have shown the synthetic potential and versatility of glycals leading to novel polyhydroxylated lactams and piperidines. The target compounds **4**, **5**,



Scheme 4. *Reagents and conditions*: (a) H_2, Pd/C, AcOEt, rt, 6 h, 50%; (b) $LiAlH_4$, THF, reflux, 4 h, 50%; (c) H_2, Pd/C, EtOH, rt, 24 h, 50%.

and **16** extend the general class of known azasugars and analogues. The protocol described herein provides an easy access to the synthesis of other related azasugar analogues, and further work is in progress in our laboratory.

Acknowledgements

We gratefully acknowledge financial support from CNR and from the Deutsche Forschungsgemeinschaft (postdoctoral fellowship to H.-G.W.).

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12. Compound **4a**: $[\alpha]_D^{25}$ −19 (*c* 1.1, MeOH). ^{1}H NMR (200 MHz, D_2O): $\delta = 2.26$ (dd, $J = 18.0/2.2$ Hz, 1H, H-2); 2.85 (dd, $J = 18.0/6.6$ Hz, 1H, H-2′); 3.53 (dd, $J = 11.7/6.6$ Hz, 1H, H-6); 3.59 (dd, $J = 11.7/4.4$ Hz, 1H, H-6′); 3.65 (dd, $J = 7.2/2.2$ Hz, 1H, H-4); 3.81 (ddd, $J = 7.2/6.6/4.4$ Hz, 1H, H-5); 4.45 (dt, $J = 6.6/2.2$ Hz, 1H, H-3). ^{13}C NMR (50.3 MHz, D_2O): $\delta = 41.2$ (C-2); 64.5 (C-6); 66.8 (C-4); 71.1, 73.4 (C-3,5); 170.5 (CO).
Compound **4b**: $[\alpha]_D^{25}$ +6 (*c* 1.2, MeOH). ^{1}H NMR (200 MHz, D_2O): $\delta = 2.33$ (dd, $J = 17.6/1.7$ Hz, 1H, H-2); 2.80 (dd, $J = 17.6/6.0$ Hz, 1H, H-2′); 3.68 (dd, $J = 12.0/5.7$ Hz, 1H, H-6); 3.77 (dd, $J = 8.5/4.6$ Hz, 1H, H-4); 3.80 (dd, $J = 12.0/3.5$ Hz, 1H, H-6′); 3.93 (ddd, $J = 8.5/5.7/3.5$ Hz, 1H, H-5); 4.64 (ddd, $J = 6.0/4.6/1.7$ Hz, 1H, H-3). ^{13}C NMR (50.3 MHz, D_2O): $\delta = 41.4$ (C-2), 62.2 (C-4); 65.3 (C-6), 69.2, 71.3 (C-3,5); 174.4 (CO).
13. Compound **5a**: $[\alpha]_D^{25}$ −10 (*c* 1.1, MeOH). ^{1}H NMR (200 MHz, D_2O): $\delta = 2.38$ (dd, $J = 18.0/2.9$ Hz, 1H, H-2); 2.81 (dd, $J = 18.0/4.4$ Hz, 1H, H-2′); 3.69–3.91 (m, 3H, H-5,6,6′); 4.05 (dd, $J = 5.2/2.2$ Hz, 1H, H-4); 4.21 (ddd, $J = 5.2/4.4/2.9$ Hz, 1H, H-3);. ^{13}C NMR (50.3 MHz, D_2O): $\delta = 36.2$ (C-2); 54.9 (C-5); 62.8 (C-6); 67.6, 68.1 (C-3,4); 173.1 (CO).
Compound **5b**: $[\alpha]_D^{25}$ −18 (*c* 1.1, MeOH). ^{1}H NMR (200 MHz, D_2O): $\delta = 2.48$ (dd, $J = 18.3/5.1$ Hz, 1H, H-2); 2.70 (dd, $J = 18.3/4.4$ Hz, 1H, H-2′); 3.56 (dt, $J = 7.3/4.4$ Hz, 1H, H-5); 3.72 (dd, $J = 17.6/4.4$ Hz, 1H, H-6); 3.78 (dd, $J = 17.6/4.4$ Hz, 1H, H-6′); 3.95 (dd, $J = 7.3/2.2$ Hz, 1H, H-4); 4.22 (ddd, $J = 5.1/4.4/2.2$ Hz, 1H, H-3). ^{13}C NMR (50.3 MHz, D_2O): $\delta = 38.1$ (C-2); 57.3 (C-5); 63.8 (C-6); 67.9, 70.3 (C-3,4); 173.3 (CO).
14. For a recent asymmetric synthesis of fagomine and isomers, see: Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817–819 and references cited therein.
15. Spectral data for compound **16** were in accordance with that reported.[14]