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Synthesis of D-*gluco*-, L-*ido*-, D-*galacto*-, and L-*altro*-configured glycaro-1,5-lactams from tartaric acid

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Abstract—The D-*gluco*-, L-*ido*-, D-*galacto*-, and L-*altro*-configured glycaro-1,5-lactams **1**–**4** were prepared from the known tartaric anhydride **5** via the aldehyde **6**. These lactams are known (**1**) or potential (**2**–**4**) inhibitors of β-D-glucuronidases and α-L-iduronidases. Olefination of **6** to the (*E*)- and (*Z*)-alkenes **7** or **8**, followed by reagent or substrate controlled dihydroxylation, lactonization, azidation, reduction, and deprotection led in 10 steps and in overall yields of 11–20% to the title lactams.

β-D-Glucuronidases (EC 3.2.1.31) and α-L-iduronidases (EC 3.2.1.76) cleave β-, and α-glycuronic acid residues, respectively, from the non-reducing end of glycosaminoglycans, such as chondroitin sulfate and hyaluronic acid. These glycosidases are essential for the normal restructuring and turnover of extracellular matrix components.[1] Glycuronidases also play crucial roles in pathophysiological processes. Deficiency of β-D-glucuronidase and α-L-iduronidase in humans leads to mucopolysaccharidosis of type VII (Sly syndrome)[2] and of type I (Hurler syndrome),[3] respectively, while release of β-D-glucuronidase from cancer cells[2] and breakdown of the basement membrane are required for metastasis of adenocarcinoma. Induction of β-D-glucuronidase in the intestinal flora may also be responsible for the pathogenesis of colon cancer.[4] In addition, β-D-glucuronidase and other lysosomal enzymes are released into the synovial fluid in inflammatory joint diseases like rheumatoid arthritis and contribute to their symptoms.[5] Strong and selective inhibitors of β-D-glucuronidase and α-L-iduronidase are thus of pharmacological interest.

Considering the potential pharmacological use of glycuronidase inhibitors and the use of glycosidase inhibitors in analyzing the mechanism of action of glycosidases[6] we wished to synthesize the four diastereoisomeric glycarolactams **1**–**4** (Fig. 1). Glucarolactam **1**[7] is a well known β-D-glucuronidase inhibitor. Its synthesis by catalytic oxidation of gluconolactam (obtained from nojirimycin) requires a rather expensive Pt catalyst loading (ca. 50 wt %). A synthesis of the methyl ester of benzyl protected glucarolactam from methylglucopyranoside in 14 steps and an overall yield of 15% was also reported.[8] The glycarolactams **2**–**4** are not known.

(*R*,*R*)- and (*S*,*S*)-Tartaric acid (L- and D-threaric acid) and their derivatives were used extensively as chiral auxiliaries, resolving agents, and building blocks,[9] yet, there are few instances only where tartaric acid derivatives were used as building blocks for the synthesis of (chain extended) carbohydrates and analogues;[9] examples are the syntheses of deoxynojirimycin,[10] castanospermine,[11] polyhydroxy piperidines,[12] conduritol,[13] and a myoinositol

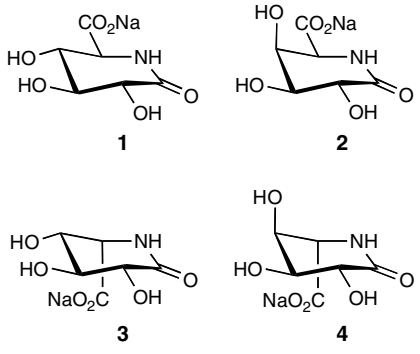

Figure 1.

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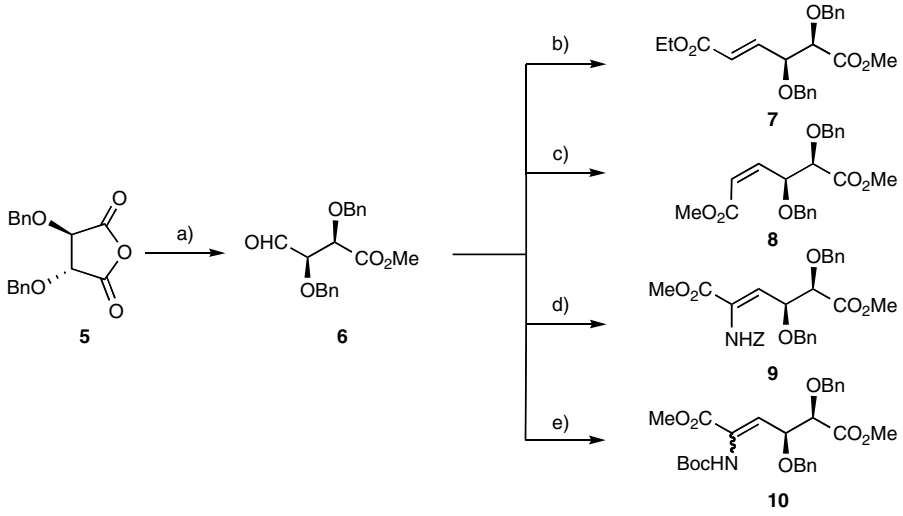
derivative.[14] We report a divergent synthesis of the glycarolactams **1**–**4** from the tartaric anhydride **5**.[15]

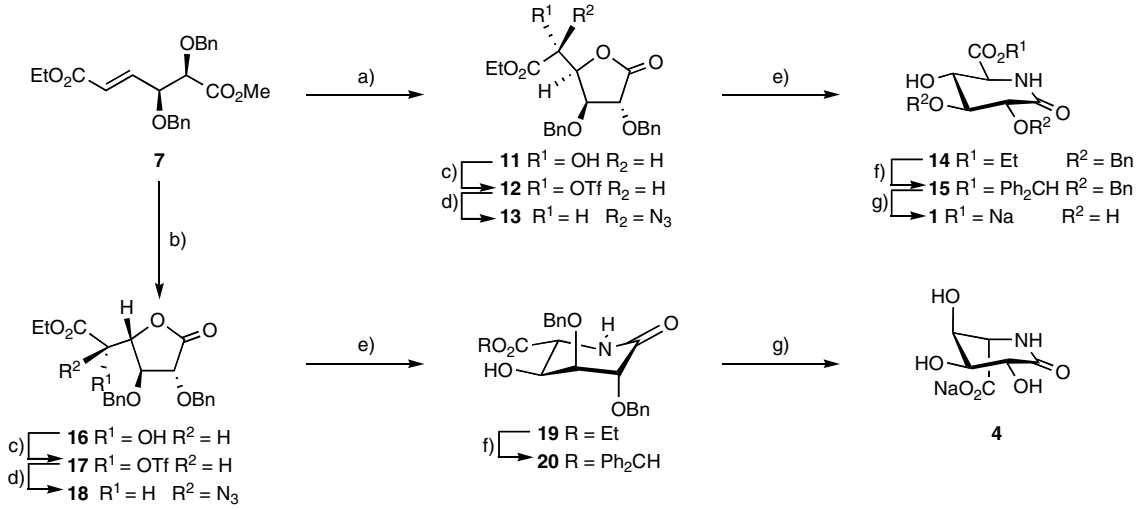
Methanolysis of the anhydride **5**[15] followed by formation of the mixed anhydride with methyl chloroformate, $ZnBH_4$ reduction, and oxidation with trichlorocyanuric acid and TEMPO[16] gave the aldehyde **6** (60% from **5**). Wittig–Horner olefination of the aldehyde **6** led to the (*E*)-alkene **7** (80%). The Still–Genari version of the Wittig–Horner olefination of **6** provided the (*Z*)-alkene **8** (75%), while olefination with the phosphonate derived from Z-protected methyl glycinate[17] provided mainly the (*Z*)-configured dehydroamino acid **9** (85%; *E*/*Z* = 1:13). The analogous olefination of **6** with the phosphonate derived from Boc protected methyl glycinate yielded 85% of a 1:1 (*E*/*Z*) mixture of the dehydroamino acids **10** (Scheme 1).

Aminohydroxylation of **7**, hydroboration of **9**, and 1,4-addition of alcoholates to the dehydroamino acids **9** and **10** failed, and starting material was recovered. However, reagent controlled dihydroxylation of **7** with OsO_4 in the presence of $NMO{\cdot}H_2O$ and $(DHQ)_2$-PHAL followed by spontaneous γ-lactonization gave selectively the L-idarolactone **11** (75%). Triflation of **11** followed by substitution with tetramethyl guanidinium azide[18] led almost quantitatively to the D-*gluco* azido lactone **13**.

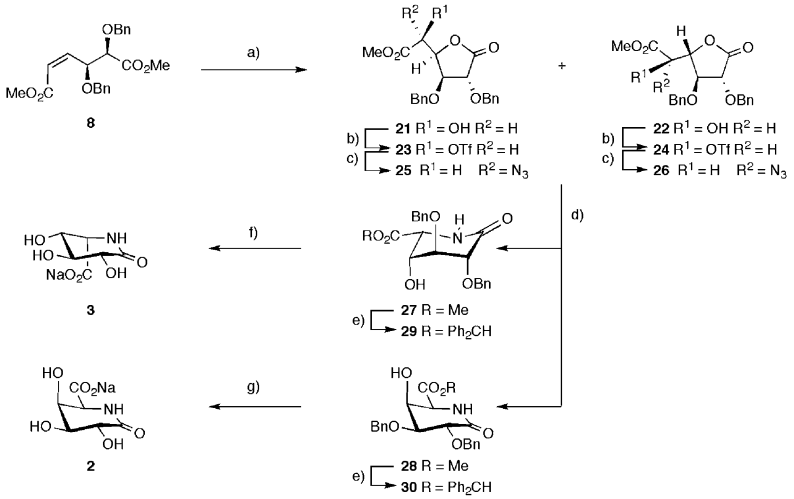
$Pd/CaCO_3$ (10%) catalyzed hydrogenation of the azide **13** in EtOH followed by spontaneous lactamization



Scheme 1. Reagents and conditions: (a) (1) MeOH; (2) $ClCO_2Me$, $^iPr_2NEt$, THF, 0 °C, then $ZnBH_4$, MeOH, 0 → 10 °C; (3) trichlorocyanuric acid, TEMPO, CH_2Cl_2, −78 → 0 °C; 60%. (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; 80%. (c) $(F_3CCH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78 °C; 75%. (d) $(MeO)_2P(O)CH(NHZ)CO_2Me$, 1,1,3,3-tetramethylguanidine, THF, −78 → 25 °C; 85% (*E*/*Z* 1:13). (e) $(MeO)_2P(O)CH(NH\text{-}Boc)CO_2Me$, DBU, THF, −0 → 25 °C; 85% (*E*/*Z* 1:1).



Scheme 2. Reagents and conditions: (a) OsO_4, $K_3[Fe(CN)_6]$, $(DHQ)_2$-PHAL, $MeSO_2NH_2$, K_2CO_3, $^tBuOH/H_2O$ (1:1), 0 °C; 75%. (b) OsO_4, $NMO{\cdot}H_2O$, acetone/H_2O (4:1); 87%. (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 → 0 °C; 93% of **12**, 94% of **17**. (d) Tetramethyl guanidinium azide, CH_2Cl_2, −90 → 0 °C; 98% of **13**, 98% of **18**. (e) $Pd/CaCO_3$, H_2 (1 bar), EtOH, 4 h then N_2, 12 h; 65% of **14**, 63% of **19**. (f) (1) $LiOH{\cdot}H_2O$, $MeOH/H_2O$ (1:1); (2) Ph_2CN_2, acetone; 85% of **15**, 84% of **20**. (g) Pd/C, H_2 (6 bar), $MeOH/H_2O$ (1:1) then ion exchange on *Dowex* 50 W X2 (Na^+); 98% of **1**, 98% of **4**.



Scheme 3. Reagents and conditions: (a) OsO_4, NMO·H_2O, acetone/H_2O (4:1); 78% of **21** and **22** (1:1). (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, $-78 \rightarrow 0$ °C; 65% of **23** and **24** (1:2), 23% of **21**. (c) Tetramethyl guanidinium azide, CH_2Cl_2, $-90 \rightarrow 0$ °C; 98% of **24** and **25** (1:2). (d) Pd/$CaCO_3$, H_2 (1 bar), THF, 4 h then N_2, 12 h; 60% of **27** and **28** (1:2). (e) (1) LiOH·H_2O, MeOH/H_2O (1:1); (2) Ph_2CN_2, acetone; 85% of **29**, 83% of **30**. (f) Pd/C, H_2 (6 bar), MeOH/H_2O (1:1) then ion exchange on *Dowex* 50 W X2 (Na^+); 98% of **3**, 98% of **2**.

provided the protected D-glucarolactam **14** (65%). Saponification of **14** led under all conditions tested to a mixture of C(5) epimeric lactams, which was treated with Ph_2CN_2. Chromatography and crystallization gave the D-*gluco* and L-*ido* configured benzyhydryl esters **15** (85%) and **29** (12%), respectively (Scheme 2).

Substrate controlled dihydroxylation of **7** with OsO_4 and NMO·H_2O followed by lactonization gave the D-galactarolactone **16** besides some **11** (98:2, 87%). Triflation of **16** followed by azidation, reduction, saponification, and treatment with Ph_2CN_2 (Scheme 2) resulted in the L-*altro* and the D-*galacto* configured glycarolactams **20** (49%) and **30** (7%).

The D-*galacto* and L-*ido* glycarolactams **2** and **3** were synthesized from the (*Z*)-alkene **8** following the same strategy as described above. However, not too surprisingly,[19] substrate control of the dihydroxylation of the (*Z*)-alkene was not selective, and treatment of **8** with OsO_4 and NMO·H_2O afforded a 1:1 mixture (78%) of the D-*gluco* and L-*altro* lactones **21** and **22**. This mixture was subjected to the same sequence of reactions as described above for the transformation of **16**, to afford, after chromatography, the L-*ido* and the D-*galacto* glycarolactams **27** (13%) and **28** (25%). Saponification of the lactams **27** and **28** was again unavoidably accompanied by partial epimerization at C(5). Treatment of the resulting two pairs of isomeric acids with Ph_2CN_2 followed by chromatography and crystallization of the resulting benzyhydryl esters provided the protected L-*ido* and D-*galacto* glycarolactams **29** (85%) and **30** (83%) besides minor amounts of their epimers **15** and **20** (Scheme 3).

Each one of the diastereoisomeric lactams **15**, **30**, **29**, and **20** was deprotected by hydrogenolysis (aq MeOH, 6 bar) in the presence of Pd/C (10%). The resulting acids were converted to the configurationally stable sodium salts **1**–**4** by passage through a column of *Dowex* 50 W X2 (Na^+).

In conclusion, we have developed a synthesis of glycaro-1,5-lactams in 10 steps from the tartaric anhydride **5** in overall yields of 11–20%. Inhibition by **1**–**4** of β-D-glucuronidases and α-L-iduronidases and experimental details will be published elsewhere.

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