Kinetic and thermodynamic azides from α-triflates of γ-lactones: intermediates for the incorporation of polyhydroxylated D- and L-α-aminoacids into combinatorial libraries

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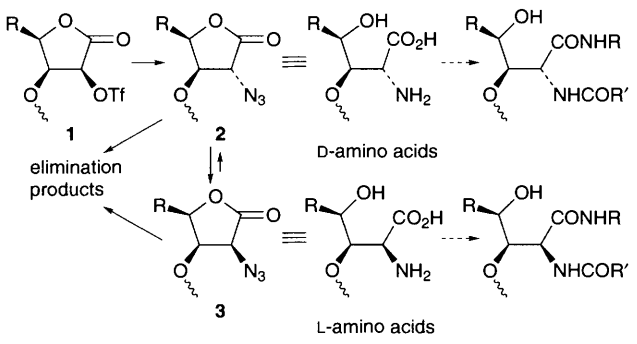
Displacement of α-triflates of 2,3,4-all *cis*-substituted γ-lactones by sodium azide in DMF gives kinetically an azide with inversion of configuration at the C-2 of the lactone; under the reaction conditions, the initially formed azide epimerises to the apparently more crowded and thermodynamically stable all *cis*-azide, giving intermediates which should readily allow the incorporation of polyhydroxylated amino acids into combinatorial libraries.

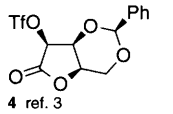
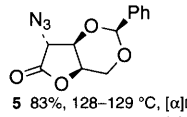
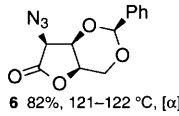
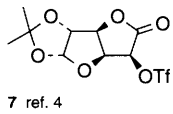
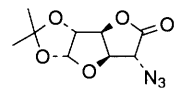
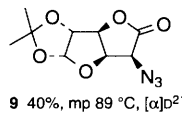
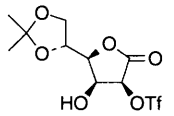
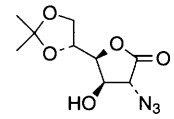
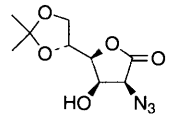
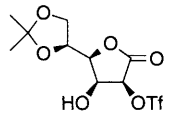
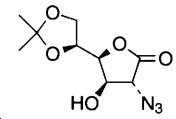
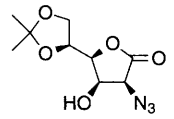
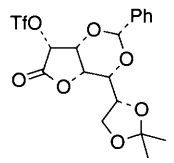
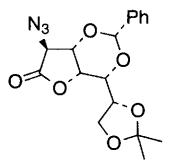
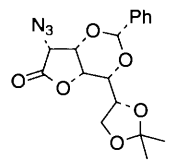
Sugar lactones are versatile starting materials for a wide range of complex targets by routes which require little or no protection.[1] There are a large number of readily available and cheap 1,4-lactones in which a *cis*-diol unit at C-2 and C-3 is also *cis* to a carbon side chain at C-4. Such materials may easily be converted in one or two steps into (usually) stable triflates **1** in which the C-3 hydroxy group may remain unprotected; lactones containing the D-*lyxo* configuration **1** and the L-*lyxo* configuration are readily available. Reaction of **1** with sodium azide in dimethylformamide gives the inverted azides **2** in high yields and such materials have been used for the synthesis of highly functionalised amino acids, Scheme 1.[2] Here we report that longer reaction times can also provide direct access to azides **3** in which the configuration at C-2 has been retained; previously such materials were obtained by much longer routes in which the configuration at C-2 had first been inverted—such complications in a synthesis are unnecessary. Studies on equilibration of the *xylono*-azides **2** suggest that the apparently more crowded *lyxono*-azides **3** are thermodynamically more stable. Lactones such as **2** and **3** are the equivalents of polyhydroxylated D- and L-amino acids, respectively; the azido lactones themselves are susceptible to direct nucleophilic ring opening by amines and thus are ideal building blocks for incorporation of novel hydrophilic amino acids into combinatorial libraries.

Examples of the utility of the subsequent equilibration of the kinetically formed azide into the all *cis*-azide are shown in Table 1. Addition of sodium azide to the triflate **4** after 50 min at room temperature afforded the azide **5** in 83% yield as the only isolated product; when the reaction mixture was left for longer, only traces of **6** were formed with the major pathway being elimination from the azide **5**. In sharp contrast, if pyridinium toluene-*p*-sulfonate (PPTS) were also added to the reaction mixture, after 3 d the azide **6** with overall retention at C-2 could be isolated in 82% yield, together with 15% of **5**. The role of PPTS in suppressing the elimination is not clear but may be due to some buffering effect of the azide base. The equilibration of pure **5** and **6** were studied; addition of sodium



Scheme 1

Table 1 Kinetic and thermodynamic azides from displacements of 2-*O*-trifluoromethanesulfonates (triflates) of 2-hydroxy-1,4-lactones in dimethylformamide[a]

Starting material	Kinetic product	Thermodynamic product
 **4** ref. 3	 **5** 83%, 128–129 °C, $[\alpha]_D^{23}$ +179.1 (*c* 1.0, Me_2CO)	 **6** 82%, 121–122 °C, $[\alpha]_D^{24}$ +37.4 (*c* 1.0, Me_2CO)
 **7** ref. 4	 **8** 83% in ref. 4	 **9** 40%, mp 89 °C, $[\alpha]_D^{21}$ +25.1 (*c* 0.56, $CHCl_3$)
 **10** mp 109–110 °C $[\alpha]_D^{21}$ +13.6 (*c* 1.00, $CHCl_3$)	 **11** 90% 120–121 °C $[\alpha]_D^{21}$ +200.3 (*c* 1.00, $CHCl_3$)	 **12** 82% 118–119 °C $[\alpha]_D^{21}$ −76.9 (*c* 1.00, $CHCl_3$)
 **13** mp 104–105 °C $[\alpha]_D^{25}$ +16.8 (*c* 0.85, $CHCl_3$)	 **14** 71%, mp 69–72 °C, $[\alpha]_D^{21}$ +165.6 (*c* 0.8, $CHCl_3$)	 **15** 46%, mp 166–168 °C, $[\alpha]_D^{21}$ −23.7 (*c* 0.35, $CHCl_3$)
 **16** ref. 6	 **17** 79%, mp 125–130 °C, $[\alpha]_D^{23}$ −153.3 (*c* 0.63, $CHCl_3$)	 **18** 66%, mp 119–121 °C, $[\alpha]_D^{23}$ −71.6 (*c* 0.56, $CHCl_3$)

[a] Satisfactory microanalytical and spectral data have been obtained for all new compounds. The stereochemistry of the azides was determined either by relation to known materials, or by single crystal X-ray crystallographic analysis of the azide or a derivative therefrom.

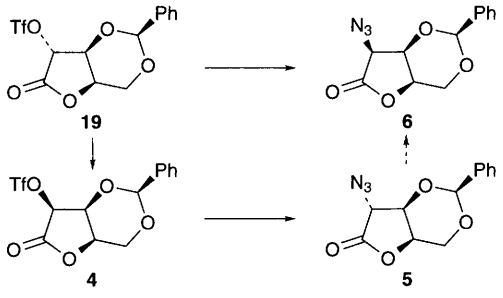
azide to either azide resulted mostly in elimination products, whereas a mixture of sodium azide and PPTS caused equilibration of the two azides. The ratio of **6** : **5** starting from **5** was 6 : 1, whereas starting from **6** the ratio was 12 : 1 thus, clearly the all *cis*-azide **6** is thermodynamically more stable than **5**.

Some lactones are more prone to elimination than others; reaction of the triflate **7**[3] with sodium azide at −20 °C gives **8** in 83% yield. Treatment of **7** with sodium azide at 0 °C gave after 2.5 h the azide **9**[4] with retention of configuration during the displacement in 39% yield, together with 9% of **8**. Both **8** and **9** are sensitive to azide induced elimination; however, a moderately effective equilibration of **8** with PPTS and sodium azide allows isolation of 56% of **9**, together with 9% of **8** remaining.

It is not necessary to protect the C-3 *cis*-OH function adjacent to the triflate, and such systems are usually less prone to elimination reactions than those in which the C-3 OH is protected. Thus the triflate **10**, derived from D-mannose, gave the gluco-azide **11** in 90% yield after 25 min at room temperature; reaction of **10** with a small excess of sodium azide over 40 h afforded the epimeric manno-azide **12** in 82% yield (together with 6% of **11**). Similar, but lower yielding results, were obtained from triflate **13**, available in two steps from L-gulonolactone, to allow the easy preparations of the epimeric azides **14** and **15** in yields of 71 and 46%, respectively.

A further example of the reaction applied to a differently protected sugar with the lactone ring in a different conformation is provided by the triflate **16**.[5] Reaction of **16** with sodium azide gave the inverted azide **17** in 79% (with 11% of **18**) after 1 h at room temperature whereas after 22 h **18** was obtained in 66% yield, together with **17** in 26% yield. Again the azides **17** and **18** are sensitive to base; **17** may be equilibrated by treatment with sodium azide in the presence of PPTS to afford **18** in 88%.

The reaction of the triflate **19**[6] epimeric with **4** with sodium azide in DMF was studied by NMR, since the benzylidene proton singlets† in **4**, **5**, **6** and **19** are all easily distinguished (Scheme 2); there is an immediate reaction of sodium azide in which some S_N2 displacement of triflate from **19** gives **6** directly, accompanied by significant epimerisation of **19** to the apparently more stable triflate **4**. Subsequently **4** undergoes S_N2 displacement to give **5**; very little epimerisation of **5** to **6** under these conditions and time would be expected. Considerable caution therefore has to be exercised in interpreting displacements of triflates of 1,4-lactones in these circumstances.



Scheme 2

Equilibrations of all the epimeric product azides with PPTS and sodium azide were investigated and the approximate values for the equilibrium constants were consistently in the range of 6 : 1 to 20 : 1. Precise values are not easy to ascertain because of some competing elimination reactions; the energy difference between two epimers for a 20 : 1 ratio is only about 4 kJ mol^{-1}, so that it would not be helpful to discuss rationales for the equilibrium position. However, the above procedure is useful for preparing reasonable quantities of epimeric azidolactones by short and experimentally easy sequences. The relative stability of the all-*cis* substituted γ-lactones is paralleled with a similar observation of the relative stability of the all-*cis* substituted δ-lactones,[7,8] although the reasons affecting the relative thermodynamic stabilities may well be different.

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Footnote

† The ^1H NMR chemical shifts δ_H for the benzylidene singlets (PhCH) in **4**, **5**, **6** and **19** are δ 5.95, 5.84, 5.89 and 5.98 respectively.

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