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Potential Intermediates for Incorporation of Polyhydroxylated Prolines into Combinatorial Libraries

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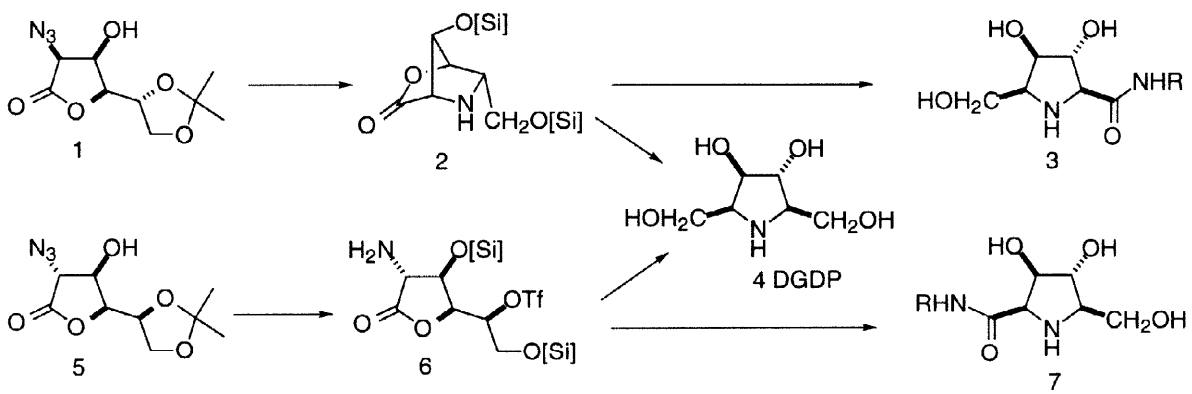
Abstract: Bicyclic **2** and monocyclic **6** 2-amino-1,4-lactones provide divergent intermediates for subsequent incorporation of polyhydroxylated prolines into combinatorial amide libraries. The X-ray crystal structure of an azidolactone, combined with molecular modelling, rationalises the very different behaviour of two azidolactones which are epimeric at a remote side-chain carbon. The conversion of **2** and **6** into DGDP **4** secures the structural claims in the paper. The enantiomers of **2** and **6** may provide access to libraries of potential inhibitors of UDP-Gal mutase and thus of mycobacterial cell wall biosynthesis.

Proline has a major role in inducing secondary structure in peptide sequences, and novel amide libraries might be generated from suitably protected and activated precursors to hydroxylated prolines. Hydroxyprolines have been shown to significantly influence polypeptide secondary structure in antibiotics and have been synthetically useful intermediates in approaches to naturally occurring alkaloids.[1] This paper describes the use of the readily accessible azidolactones **1** and **5** to generate bicyclic **2** and monocyclic **6** lactones respectively which are convenient units for the generation of amide libraries since both undergo nucleophilic attack by amines to give amides such as **3** and **7**; in each case the proline ring is formed by nucleophilic ring closure of an amine at C-2 of the lactone by displacement of a triflate at C-5. The intermediates **2** and **6** may also be of value in the synthesis of aminosugars, and their structures are firmly established by conversion to DGDP **4**.



The synthesis of the bicyclic lactone **2** is shown in Scheme 1. 2-*O*-Triflates of γ-lactones may be converted in high yields to either kinetic or thermodynamic azides.[2] Thus, azide displacement of the triflate **8**, derived from D-mannose, under kinetic conditions gave the C-2 inverted *gluco* azide **11** whereas under thermodynamic conditions the *manno* azide **1** was formed with overall retention of configuration at C-2 of the lactone in good yield. Alternatively **1** may be prepared from the open chain azidoester **10**, readily derived from D-glucono-1,5-lactone as previously described,[3] by hydrolysis in aqueous trifluoroacetic acid to give the γ-lactone **9** m.p. 174-175°C (decomp.), $[\alpha]_D^{23}$ +27.1 (*c*, 1.0 in H_2O) [96% yield]; subsequent protection of the side chain diol as its acetonide by treatment with acetone and camphor sulfonic acid afforded **1** in 91% yield. The absolute configuration of **1** has been determined by X-ray crystallographic analysis [Figure1].[4]

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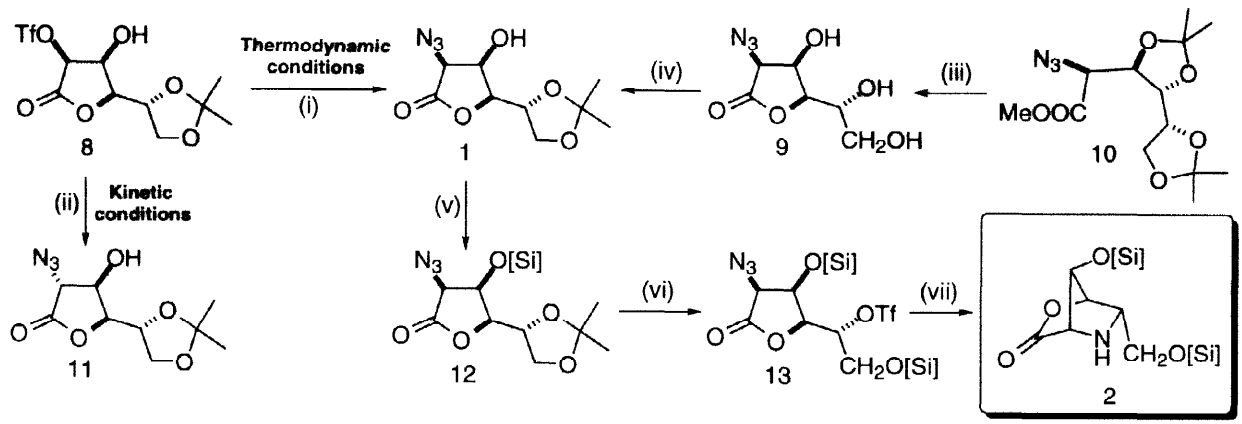
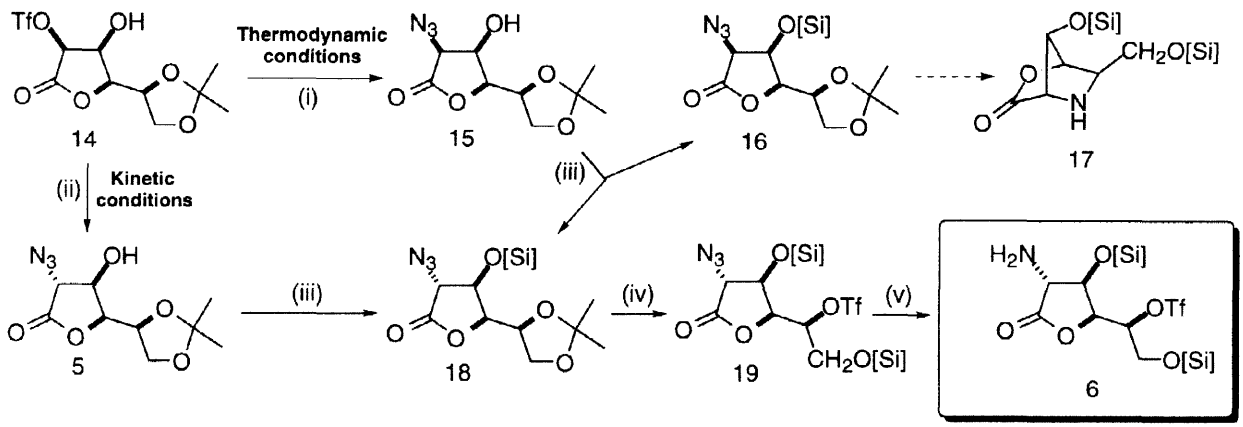


Scheme 1: (i) 1.2 eq. NaN_3, DMF, 40h, 82% (ii) 1.0 eq. NaN_3, DMF, 25 min, 90% (iii) TFA / H_2O (3:2), 96% (iv) Acetone, CSA, 91% (v) TBDMSOTf, pyridine, CH_2Cl_2, 75% (vi) a)AcOH / H_2O (4:1), 84% b)TBDMSCl, imidazole, DMF, 71% c)Tf_2O, pyridine, CH_2Cl_2, 95% (vii) H_2, Pd-black, EtOAc then NaOAc, CH_3CN, 86%

Protection of the C-3 hydroxyl of the *manno* azide **1** as its silyl ether was effected with *tert*-butyldimethylsilyl triflate and pyridine in dichloromethane to yield **12** m.p. 115-116°C, $[\alpha]_D^{20}$ -42.0 (*c*, 1.0 in $CHCl_3$) [75%]. Removal of the side chain acetonide in **12** with acetic acid and water gave a diol which upon treatment with *tert*-butyldimethylsilyl chloride and imidazole in DMF afforded selective protection of the primary C-6 hydroxyl. Subsequent esterification of the remaining free C-5 hydroxyl function with trifluoromethanesulfonic anhydride and pyridine in dichloromethane gave the stable triflate **13** m.p. 78-80°C, $[\alpha]_D^{22}$ -8.7 (*c*, 1.0 in $CHCl_3$) in 57% yield from **12**. Reduction of the azide **13** in ethyl acetate with hydrogen in the presence of palladium black gave a non-isolable C-2 amine which underwent spontaneous intramolecular SN2 displacement of the C-5 triflate to afford the [2.2.1] bicycle **2** as the free amine and its triflate salt. Treatment of the crude mixture with sodium acetate in acetonitrile gave the free amine **2**[5] in which the pyrrolidine ring is established, as the sole product in 86% yield [37% overall yield from **1**].



Scheme 2: (i) 3.0 eq. NaN_3, DMF, 48h, 46% (ii) 0.97 eq. NaN_3, DMF, 2.5 h, 75% (iii) TBDMSOTf, pyridine, CH_2Cl_2, 85% (**18** from **5**), 62% (**16** and **18** from **15**) (iv) a)AcOH / H_2O (4:1), 99% b)TBDMSCl, imidazole, DMF, 76% c)Tf_2O, pyridine, CH_2Cl_2, 95% (v) H_2, Pd-black, EtOAc, 99%

A very similar – but unsuccessful - strategy [Scheme 2] was adopted for the synthesis of the bicyclic lactone **17** [epimeric at C-5 of the sugar with **2**] which should be formed by an identical sequence from **15**. The azidolactone **15** is epimeric at C-5 with **1** and it was anticipated in the early stages of the sequence that the chemistry should not be much affected by the remote C-5 stereochemistry. As expected, azide displacement of the 2-*O*-triflate **14**, derived from L-gulono-1,4-lactone,[6] under kinetic conditions gave the *ido*-azide **5** and the *gulo* azide **15** in which the stereochemistry at C-2 is retained, under thermodynamic conditions. However, silylation of the C-3 hydroxyl of the *gulo* azide **15** proved surprisingly inefficient under a wide set of conditions, proceeding to give complex reaction mixtures. Treatment with *tert*-butyldimethylsilyl triflate and pyridine in

dichloromethane yielded the C-3 hydroxyl protected *gulo* azide **16** [32%], together with the epimerised C-3 protected *idono* azide **18** [30%] and elimination products. The *gulo* azide **15** differs from the *manno* azide **1** only in the absolute configuration at C-5; such an apparently trivial change in remote stereochemistry would not be expected to have such a profound effect on the reactivity at C-3.

Molecular modelling studies provide an rationale for this reactivity difference. The Sybyl Version 6.3 molecular modelling package and the Tripos force field[7] were used to calculate the most stable conformers of the two thermodynamic azides **1** and **15**. The C4-C5 bond was rotated in 30° increments (torsion angle was defined in terms of O(lactone)-C4-C5-O). For the *manno* azide **1**, there was essentially only one broad low energy region between 120°-210°. Full geometry optimization within this range resulted in a structure [Figure 2], very similar to that determined by X-ray diffraction [Figure 1].[4] In contrast, the *gulo* azide **15** could adopt two low energy conformations corresponding to torsion angle ranges of 60°-90° and 240°-330°. Full geometry optimization yielded a lowest energy conformation corresponding to a torsion angle of 305° [Figure 3]. It is clear that in the *gulo* azide **15** the C-3 hydroxyl is more hindered and much less accessible to bulky protecting groups. In addition, the C-3 hydroxyl group on the *gulo* azide **15** is suitably oriented to form a hydrogen bond with the oxygen in the second ring in low polarity environments. If such a hydrogen bond forms, it would further stabilise this low energy conformation. The ^{1}H NMR spectra of the two azides is consistent with this explanation. The chemical shifts of all protons are similar with the exception of the C-3 hydroxyl proton which is considerably downfield shifted (δ 3.21) in the *gulo* azide **15** compared with the *manno* azide **1** (δ 2.69).

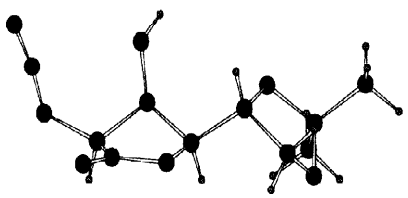


Figure 1: X-ray Crystal Structure of manno-azide 1

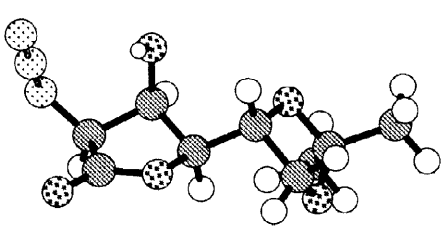


Figure 2: Low energy conformation of manno-azide 1

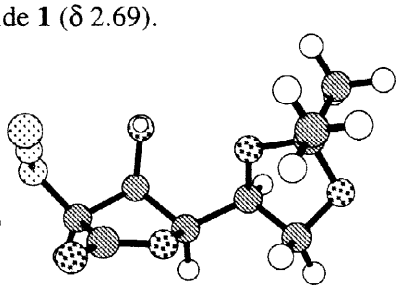
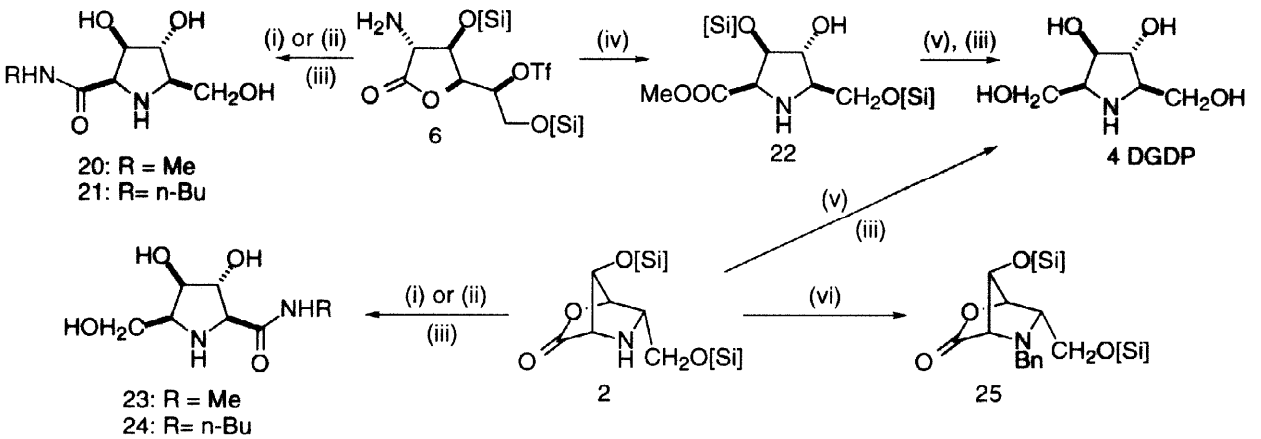


Figure 3: Low energy conformation of gulo-azide 15

Silylation of the relatively less hindered *idono* azide **5** proved straightforward [Scheme 2]. Treatment with *tert*-butyldimethylsilyl triflate and pyridine in dichloromethane gave the fully protected azido lactone **18** $[\alpha]_D^{22}$ +117.5 (*c*, 0.55 in $CHCl_3$) in 85% yield. Sequential treatment of **18** with aqueous acetic acid, *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide, and triflic anhydride and pyridine afforded the C-5 triflate **19** $[\alpha]_D^{23}$ +89.6 (*c*, 0.75 in $CHCl_3$) in an overall yield of 71%. Reduction of the azide by hydrogenation in ethyl acetate over palladium black yielded the monocyclic amino triflate **6**[8] in 99% yield. Bicyclic ring closure across the γ-lactone in **6** is not possible due to the *trans* nature of the C-2 amine and the C-4 side chain; nonetheless, the unexpected stability of the aminotriflate in which intermolecular oligomerisations must be relatively slow make this an attractive intermediate for the synthesis of amide libraries such as **7**.

The potential of the aminotriflate **6** and the bicyclic lactone **2** in incorporating hydroxyprolines into amide libraries was validated by ring opening reactions of the lactones with amines. Reaction of the amino triflate **6** with methylamine [Scheme 3] gave initial ring opening of the lactone to an aminoamide which underwent spontaneous cyclisation to form a pyrrolidine ring; subsequent removal of the silyl groups by treatment with hydrogen chloride in methanol afforded the novel hydroxylated proline methylamide **20** $[\alpha]_D^{23}$ +65.6 (*c*, 0.8 in H_2O) [2 steps, 97% yield]. Treatment of **6** with *n*-butylamine and removal of the silyl groups gave the butylamide **21** $[\alpha]_D^{23}$ +43.1 (*c*, 0.8 in H_2O) in 92% yield. Similarly, ring opening of the bicyclic lactone **2** with methylamine and *n*-butylamine in THF followed by deprotection afforded the novel pyrrolidine amides **23** $[\alpha]_D^{23}$ -4.3 (*c*, 0.675 in H_2O) and **24** $[\alpha]_D^{23}$ +10.3 (*c*, 0.475 in H_2O) [2 steps, 80% and 86% respectively].



Scheme 3: (i) $MeNH_2$, THF (ii) $^nBuNH_2$, THF (iii) 1% HCl in MeOH, 97% (**20**), 92% (**21**), 80% (**23**), 86% (**24**), 90% (**4** from **22**), 78% (**4** from **2**) (iv) NaOAc, MeOH, 74% (v) $LiHBEt_3$, THF (vi) BnBr, NaOAc, CH_3CN, 92%

The nitrogen in **2** may also be functionalised prior to ring opening; for example, reaction of **2** with benzyl bromide and sodium acetate in acetonitrile gave the *N*-benzylated [2.2.1] bicycle **25** $[\alpha]_D^{23}$ +37.6 (*c*, 0.7 in $CHCl_3$) [92%], highlighting an additional centre of diversity through the nucleophilicity of the pyrrolidine amine.

Both **2** and **6** may be converted into DGDP **4**. Treatment of the amino triflate **6** with sodium acetate in methanol gave an aminoester which spontaneously cyclised to the proline ester **22** $[\alpha]_D^{25}$ -6.7 (*c*, 0.5 in $CHCl_3$) [74%]. Reduction of the ester **22** with lithium triethylborohydride in THF and subsequent removal of the silyl protecting group gave the known xylose isomerase[9] inhibitor DGDP **4** (2 steps, 90% yield);[10] (data consistent with that previously reported). Reduction of the bicyclic lactone **2** with lithium triethylborohydride in THF and subsequent removal of the silyl ethers also gave DGDP **4** (2 steps, 78%). These reactions confirm the structures of **2** and **6** and provide flexible syntheses of DGDP which may be utilised for a number of analogues. The mirror image of DGDP is an inhibitor of UDP-Gal mutase and mycobacterial galactan biosynthesis; the enantiomers of both **2** and **6** would be readily available starting from the available sugars lactones L-mannonolactone and D-gulonolactone respectively and may provide libraries of materials to search for inhibitors of mycobacterial cell wall biosynthesis in a novel approach to the treatment of tuberculosis.[11]

In summary, this paper reports an efficient synthesis of a [2.2.1] bicyclic lactone **2** and a related monocyclic lactone **6**; the lactone functionality of these divergent intermediates is readily attacked by amines leading to a novel class of polyhydroxylated proline derivatives which may be used for the incorporation into combinatorial libraries. In addition a surprising difference in reactivity between two azido lactones which differ only in the configuration of a remote protected oxygen has been rationalised by molecular modelling.[12]

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[4] Details of the crystal structure of **1** will be reported in a full paper.

[5] Selected data for [2.2.1] bicycle **2**; $[\alpha]_D^{25}$ +10.4 (*c*, 1.35 in CH_3CN); δ_H (CD_3CN): 0.08, 0.13, 0.14 (12H, 3 x s, 2 x $Si(C\underline{H}_3)_2$), 0.91, 0.91 (18H, 2 x s, 2 x $SiC(C\underline{H}_3)_3$), 2.32 (1H, NH), 3.43 (1H, b-d, H-2), 3.53 (1H, a-t, H-6), 3.57 (1H, m, H-5), 3.67 (1H, dd, $J_{6',5}$ 5.1 Hz, $J_{6',6}$ 9.0 Hz, H-6'), 4.28 (1H, b-d, H-3), 4.62 (1H, b-t, H-4); δ_C (CD_3CN): -5.4, -5.3, -4.9, -4.9 (4 x q, 2 x $Si(\underline{C}H_3)_2$), 18.4, 18.8 (2 x s, 2 x $Si\underline{C}(CH_3)_3$), 25.8, 26.1 (2 x s, 2 x $SiC(\underline{C}H_3)_3$), 62.1 (t, C-6), 59.1, 63.5, 75.7, 82.1 (4 x d, C-2, C-3, C-4, C-5), 173.7 (s, C=O).

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[8] Selected data for amino triflate **6**; $[\alpha]_D^{24}$ +50.0 (*c*, 0.55 in $CHCl_3$); δ_H ($CDCl_3$): 0.10, 0.10, 0.19, 0.20 (12H, 4 x s, 2 x $Si(C\underline{H}_3)_2$), 0.90, 0.95 (18H, 2 x s, 2 x $SiC(C\underline{H}_3)_3$), 3.83 (1H, d, $J_{2,3}$ 8.2 Hz, H-2), 3.90 (2H, m, H-6, H-6'), 4.49 (1H, a-t, H-3), 4.86 (1H, dd, $J_{4,3}$ 7.8 Hz, $J_{4,5}$ 2.2 Hz, H-4), 5.21 (1H, ddd, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 8.0 Hz, H-5); δ_C ($CDCl_3$): -5.4, -5.3, -4.8, -4.1 (4 x q, 2 x $Si(\underline{C}H_3)_2$), 18.6, 18.8 (2 x s, 2 x $Si\underline{C}(CH_3)_3$), 26.1, 26.1 (2 x s, 2 x $SiC(\underline{C}H_3)_3$), 62.1 (t, C-6), 58.7, 76.1, 77.6, 88.0 (4 x d, C-2, C-3, C-4, C-5), 119.3 (q, CF_3), 176.4 (s, C=O).

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