Pergamon

*Tetrahedron Letters*, Vol. 35, No. 47, pp. 8891-8894, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01931-2

# Polyhydroxylated Cyclohexane and Cyclopentane α-Amino Acids from Cyclisations of an Azidolactone

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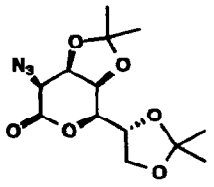
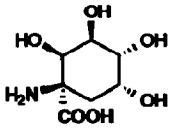
**Abstract:** Short routes to tetrahydroxylated cyclohexane and cyclopentane α-amino acids with control of the stereochemistry at all 5 carbons bearing functional groups are described from an azidolactone.

α, α-Disubstituted α-amino acids induce secondary structure in short peptide sequences;[1] the azidolactone **1**[2] has been used in the synthesis of α-amino acid derivatives in which the α carbon is also the anomeric carbon of mannofuranose allowing the incorporation of such materials into oligopeptides.[3] This paper shows that **1** can give ready access to a further class of α-amino acids, illustrated by the preparations of the polyhydroxylated cyclohexane α-amino acid **2** and of the cyclopentane α-amino acids **3** and **4**.



**1**



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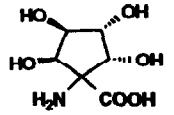

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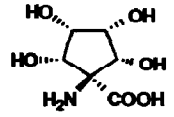
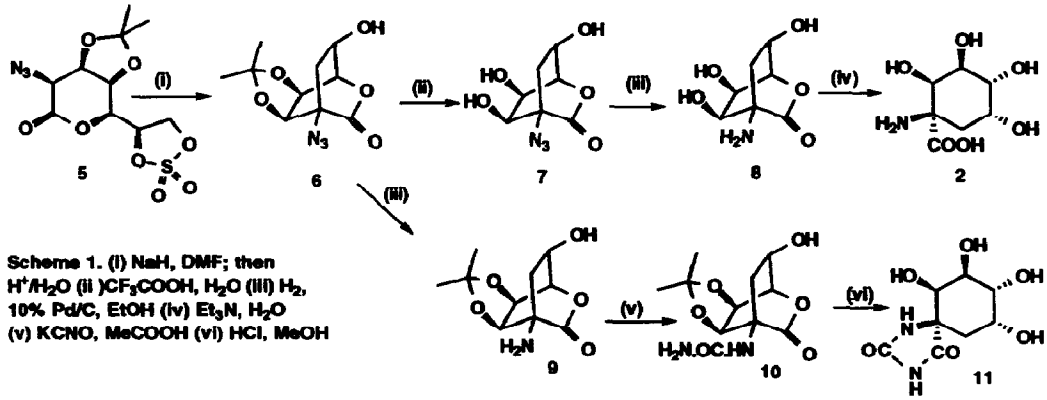


**4**

For the synthesis of the cyclohexane amino acid **2**, the diacetonide **1** was converted to the azidosulphate **5** in 92% yield as previously described.[4] Treatment of the azidosulphate **5** with sodium hydride in N,N-dimethylformamide induced cyclisation by attack of the carbanion derived from proton removal at C-2 in a 6-*exo*-tet process onto the primary centre of the sulphate; subsequent hydrolysis of the intermediate bicyclic sulphate by sulphuric acid afforded the bicyclic azidolactone **6**, oil, $[\alpha]_D^{20}$ +52.7 (*c*, 1.0 in $CHCl_3$), in 59% yield.



**Scheme 1.** (i) NaH, DMF; then $H^+/H_2O$ (ii) $CF_3COOH$, $H_2O$ (iii) $H_2$, 10% Pd/C, EtOH (iv) $Et_3N$, $H_2O$ (v) KCNO, MeCOOH (vi) HCl, MeOH

Removal of the isopropylidene protecting group in **6** by treatment with aqueous trifluoroacetic acid gave the azidotriol **7**,[5] m.p. 121-123°C, $[\alpha]_D^{20}$ -150.0 (*c*, 1.0 in EtOAc) in 70% yield; subsequent hydrogenation of **7** gave the unprotected aminolactone **8**, m.p. >200°C (dec.), $[\alpha]_D^{21}$ -172.0 (*c*, 0.5 in DMSO), in quantitative yield. The lactone ring in **8** was opened by reaction with aqueous triethylamine to give the amino acid **2**[6] in 56% yield after crystallisation from water. Because of the possibility of reversible aldol condensations taking place during the ring opening of **8**, the structure of the cyclohexane amino acid **2** was firmly established by an X-ray crystallographic study.[7]

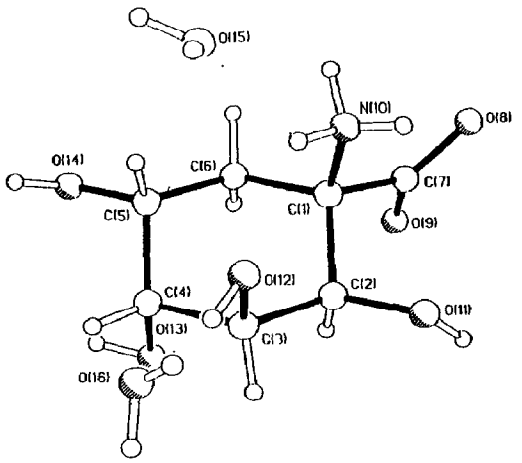
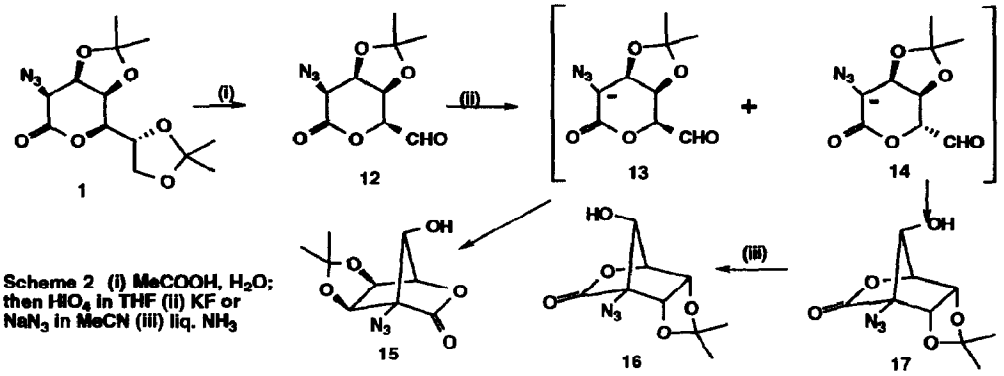



**Figure 1.** X-ray Molecular Structure of **2**, (1R,2R,3R,4R,5R)-1-Amino-2,3,4,5-tetrahydroxy-cyclohexane-1-carboxylic acid showing crystallographic numbering scheme

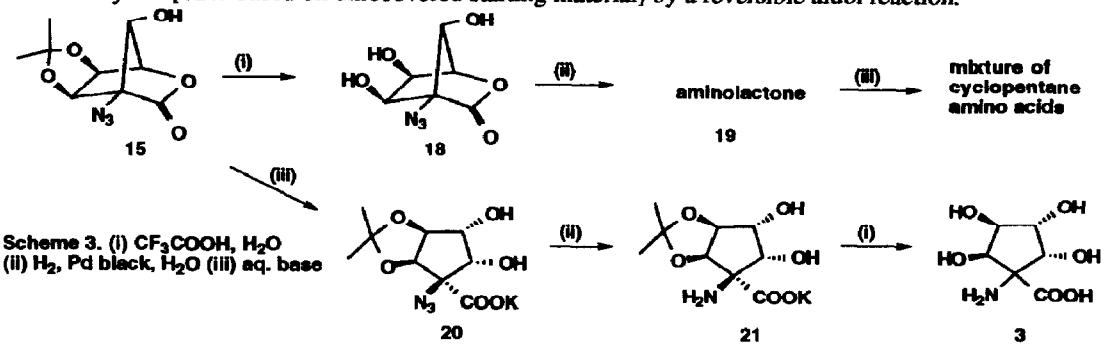
The bicyclic lactone **6** may also be used as a divergent intermediate for the efficient synthesis of pseudosugars and other very highly substituted cyclohexanes. Thus, hydrogenation of **6** in ethanol in the presence of palladium on carbon gave the protected aminolactone **9**, m.p.173-175°C; $[\alpha]_D^{21}$ +8.4 (*c*, 1.0 in EtOH) [quantitative yield] which, with potassium cyanate in acetic acid, afforded the urea **10**, m.p. 231-233°C, $[\alpha]_D^{25}$ +7.0 (*c*, 0.7 in DMF), in 87% yield. Reaction of **10** with methanolic hydrogen chloride resulted in removal of the ketal protecting group opening of the lactone ring followed by closure to the spirohydantoin **11**,[8] a cyclohexane analogue of the plant growth regulator hydantocidin,[9] in 88% yield.




**Scheme 2** (i) MeCOOH, $H_2O$; then $HIO_4$ in THF (ii) KF or $NaN_3$ in MeCN (iii) liq. $NH_3$

The synthesis of the cyclopentane amino acids **3** and **4** depends on the efficient aldol cyclisation of the azidoaldehyde **12** - easily derived from **1** - to give the azidolactones **15** and **17**.[10] Thus reaction of **12** with potassium fluoride in acetonitrile in the presence of 18-crown-6 afforded the azidolactones **15** and **17**

in a combined yield of 73% and a ratio of 4:1 with the major product **15** formed from closure of the anion **13**, use of sodium azide as the base gave a combined yield of **15** and **17** of 88% in a ratio of 1:3, with the major product **17** arising from closure of the epimeric anion **14**. Additionally, **17** is the product of kinetic closure of anion **14**; treatment of **17** with liquid ammonia gave the thermodynamically more stable lactone **16** in 63% yield [82% based on unrecovered starting material] by a reversible aldol reaction.




Scheme 3. (i) $CF_3COOH$, $H_2O$ (ii) $H_2$, Pd black, $H_2O$ (iii) aq. base

A route for the preparation of **3** from **15** was planned, analogous to that used for the transformation of **6** into the cyclohexane **2**. Aqueous trifluoroacetic acid caused removal of the ketal protecting group [Scheme 3] to give the azidotriol **18**, m.p. 134-135°C, $[\alpha]_D^{20}$ +41.7 (*c*, 1.0 in $CH_3OH$), in 89% yield. Hydrogenation of **18** gave an amino lactone **19** as a single compound, but all attempts to open **19** with aqueous base under a variety of conditions gave a mixture of amino acids in which **3** was only a minor component.

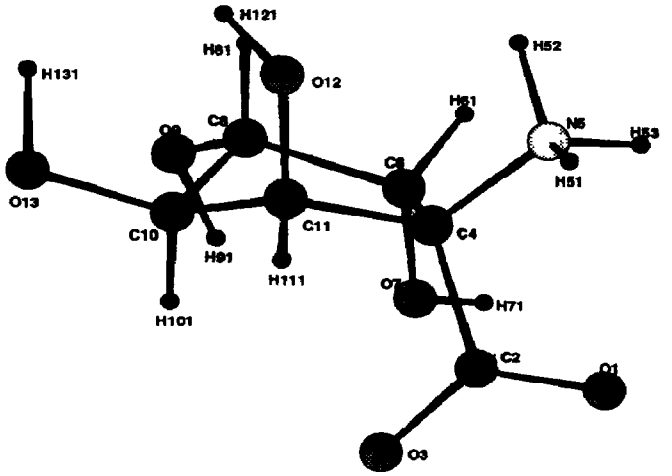
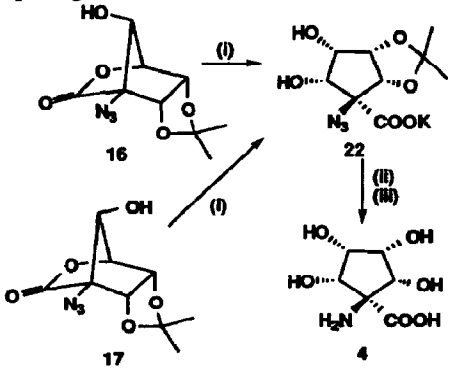



**Figure 2.** X-ray Molecular Structure of **3**, (2R,3R,4R,5R)-1-Amino-2,3,4,5-tetrahydroxycyclopentane-1-carboxylic acid with crystallographic numbering scheme

The mixture presumably arises from **19** undergoing a reversible aldol reaction cleaving the bond between the bridgehead carbon and the diol bridge[11]. In order to avoid this problem, the acetonide was removed at the end, rather than the beginning, of the sequence. Thus reaction of **15** with aqueous potassium carbonate cleanly gave the carboxylate salt **20** which was hydrogenated in the presence of palladium black to give the amine **21**; removal of the protecting group with acid afforded, after purification by ion exchange chromatography, the amino acid **3**[12] in 98% overall

yield from **15**. It was just possible that an aldol equilibration may have occurred prior/during/after the ring opening and the structure of **3** was confirmed by X-ray crystallographic analysis [Figure 2].




**Scheme 4. (i) aq. base (ii) $H_2$, Pd black, $H_2O$ (iii) $CF_3COOH$, $H_2O$**

Ring opening of azidolactone **16** with aqueous potassium carbonate gave a single potassium salt **22** which on hydrogenation of the azide to the amine and subsequent removal of the ketal protecting group gave the optically inactive highly symmetrical amino acid **4**[13] in 79% overall yield.

When the epimeric azidolactone **17** was treated sequentially with aqueous base, hydrogenated and the ketal removed, the amino acid **4** was again isolated in 55% yield; thus **17** undergoes a initial rapid aldol equilibration to the thermodynamically more stable **16** rather than ring opening.

It thus appears that aldol equilibrations of the hydroxy groups on both the one and two carbon bridges of [2.2.1] bicyclic lactones can undergo reversible aldol reactions that compete successfully with ring opening by water. This allows the synthesis under controlled conditions of a number of very highly substituted cyclopentane α-amino acids from the single azidolactone **1**; even more remarkable aldol equilibration reactions of such systems are reported in the following paper.[14]

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[3]Estevez, J. C., Estevez, R. J., Ardron, H., Wormald, M. R., Brown, D., Fleet, G. W. J., submitted for publication; Estevez, J. C., Ardron, H., Wormald, M. R., Brown, D., Fleet, G. W. J., submitted for publication.

[4]Skead, B. M., Fleet, G. W. J., Saunders, J., R. B. Lamont, R. B., *Tetrahedron Lett.*, 1993, **34**, 6115.

[5]All new compounds in this paper have spectral data and/or microanalytical data consistent with the structures proposed.

[6]Selected data for cyclohexane aminoacid **2**: m.p.>200°C (dec.). $[\alpha]_D^{21}$ +3.8 (*c*, 0.4 in DMSO); $\delta_H$ ($d_6$-DMSO) 1.70 (1H, dd, H-7, $J_{7,7'}$ 13.4 Hz, $J_{6,7}$ 3.2 Hz) 2.11 (1H, dd, H-7', $J_{6,7'}$ 9.2 Hz) 3.62 (1H, br s) 3.73 (2H, m) 4.00 (1H, br s); $\delta_C$ ($d_6$-DMSO) 33.3 (C-7) 63.9, 64.8, 67.3, 72.2, 72.2 (C-2, C-3, C-4, C-5, C-6) 173.0 (s, C-1).

[7]Atomic coordinates for the amino acids **2** and **3** are available on request from the Cambridge Crystallographic Data Centre, University Chemistry Laboratory, Lensfield Road, Cambridge CB2 1EW, UK; the crystallographic numbering system differs from that used for the same compounds elsewhere in the text. Any requests should be accompanied by the full literature citation for this paper.

[8]Selected data for spirohydantoin **11**: m.p. 248-250°C. $[\alpha]_D^{21}$ +81.6 (*c*, 0.5 in DMSO); $\delta_H$ ($d_6$-DMSO): 1.45 (1H, m, H-7) 2.01 (1H, t, H-7', J 12.5 Hz) 3.71 (1H, m) 3.75 (1H, q, J 3.9 Hz) 3.84 (1H, dd, J 2.7 Hz, J 7.6 Hz) 3.87 (1H, m) 4.50 (1H, d, OH, J 6.5 Hz) 4.85 (1H, d, OH, J 3.4 Hz) 4.90 (1H, d, OH, J 7.7 Hz) 5.37 (1H, d, OH, J 3.9 Hz) 6.64 (1H, s, NH) 10.58 (1H, s, NH); $\delta_C$ ($CD_3OD$) 34.1 (t, C-7) 63.8, 66.8, 72.4, 74.0 (4d, C-3, C-4, C-4, C-6) 67.7 (s, C-2) 159.0 (s, $NHCONH_2$) 177.9 (s, C-1).

[9]Matsumoto, M., Kirihara, M., Yoshino, T., Katoh, T., Terashima, S., *Tetrahedron Lett.*, 1993, **34**, 6289.

[10]Fairbanks, A. J., Elliott, R. P., Smith, C., Hui, A., Way, G., Storer, R., Taylor, H., Watkin, D. J., Winchester, B. G., Fleet, G. W. J., *Tetrahedron Lett.*, 1993, **34**, 7953.

[11]Reversible aldol condensations of unprotected trihydroxybicyclic lactones are discussed in the following paper: Hui,, A., Fairbanks, A. J., Nash, R. J., Lilley, P. M. de Q., Storer, R., Watkin, D. J., Fleet, G. W. J., following paper.

[12]Selected data for amino acid **3**: m.p. >215°C (dec.); $[\alpha]_D^{25}$ +22.0 (*c*, 0.15 in $H_2O$); $\delta_H$ ($D_2O$, 500 MHz): 4.02 (1H, dd, J 6.1 Hz, *J'*3.4 Hz), 4.24 (1H, br t, *J* 4.0 Hz), 4.39 (1H, d, *J* 6.1 Hz), 4.54 (1H, d, *J* 4.6 Hz); $\delta_C$ ($D_2O$, 125 MHz): 69.9 (s, C-1), 72.8, 74.8, 75.3, 77.1 (4 x d, C-2, C-3, C-4, C-5), 173.3 (s, C-6).

[13]Selected data for amino acid **4**: m.p. >225°C (dec.); $[\alpha]_D^{25}$ 0.0 (*c*, 0.45 in $H_2O$); $\delta_H$ ($D_2O$, 500 MHz): 4.10 (2H, dd, *J* 2.2 Hz, *J'*5.0 Hz), 4.15 (2H, dd, *J* 2.2 Hz, *J'*5.0 Hz); $\delta_C$ ($D_2O$ with $CF_3COOH$ at pH 1, 125 MHz): 74.5 (s, C-1), 71.8, 74.7 (2 x d, C-2, C-3, C-4, C-5), 169.2 (s, C-6).


[14]SERC CASE (to BMS), Glaxo (to AH), and SERC (to AJF) graduate awards are gratefully acknowledged.

(*Received in UK* 28 *July* 1994; *revised* 27 *September* 1994; *accepted* 30 *September* 1994)