Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8895-8898, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01932-0

Aldol Equilibrations of Unprotected Trihydroxybicyclic Lactones: Enantiomeric Tetrahydroxy-α-Aminocyclopentane Carboxylic Acids from Epimeric Bicyclic Lactones

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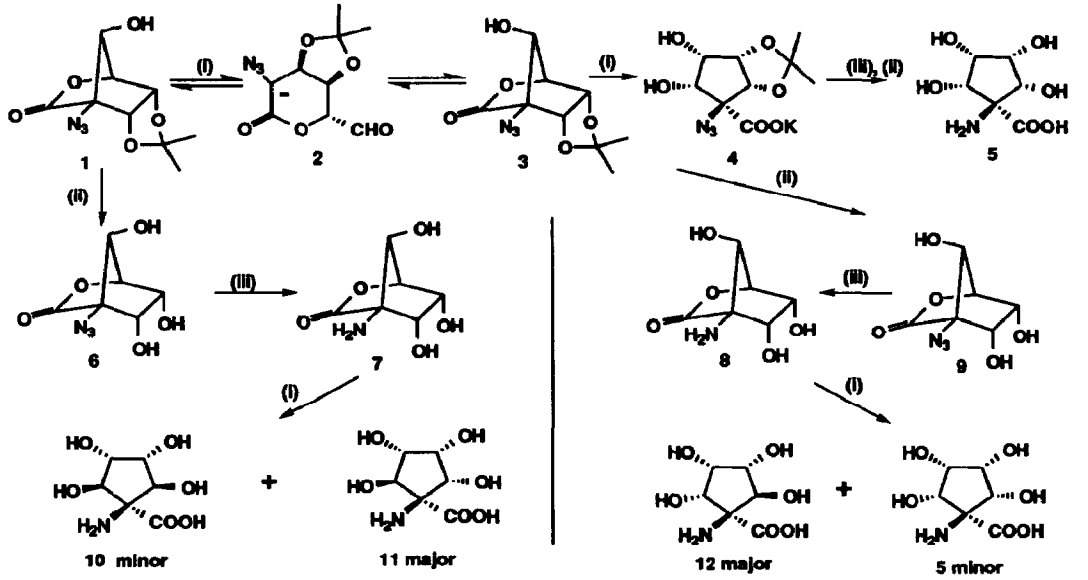
Abstract: Six stereoisomers - including an enantiomeric pair - of 1-amino-2,3,4,5-tetrahydroxy-cyclopentane-1-carboxylate have been prepared from a single azidolactone starting material by a series of remarkable aldol equilibrations.

The preceding paper[1] reported that both of the two epimeric protected bicyclic azidolactones **1** and **3** reacted with aqueous base [Scheme 1] to give the *same* azidocarboxylate **4** which on deprotection and subsequent hydrogenation of the azide function gave the optically inactive amino acid **5** as the sole isolated product. The transformation of **1** to **4** took place by equilibration *via* the anion **2** to give the more stable azidolactone **3**; subsequent attack by hydroxide then gave ring opening to **4**.



Scheme 1. (I) aq. base (II) CF_3COOH, H_2O (III) H_2, Pd black, EtOH

The amino acid **11** should be derived from directly opening the lactone ring of **1**; it was considered likely that if the azide were reduced to the amine prior to base induced ring opening of the lactone, the likelihood of aldol equilibrations would be avoided; monocyclic anions derived from **13** are likely to be less stable than **2** since an azide assists more in the stabilisation of the negative charge than an amine.

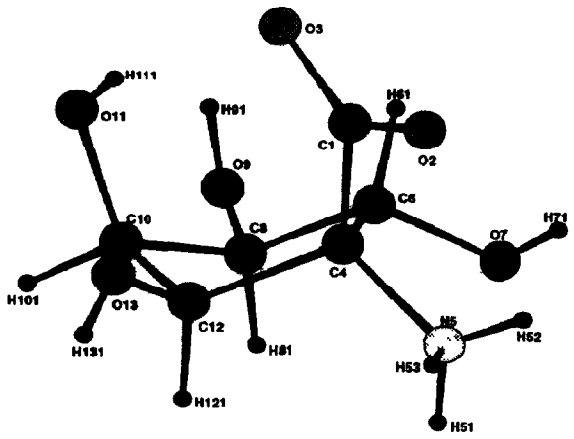
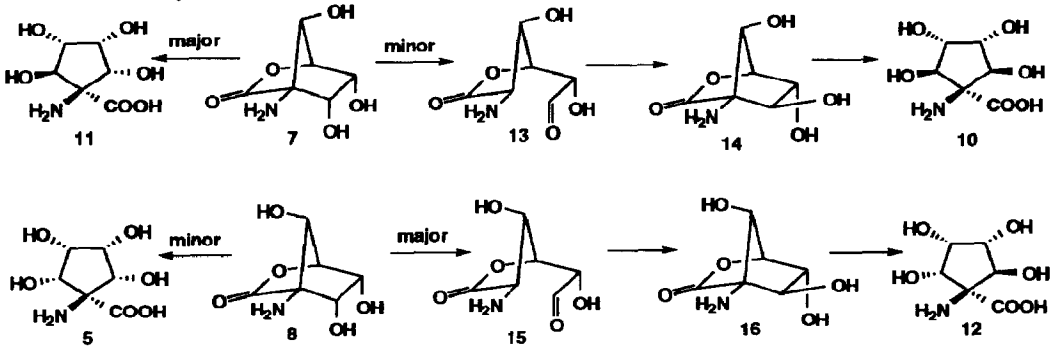


Figure 1. X-ray Molecular Structure of **11**, (1S,2R,3R,4S,5R)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane-1-carboxylic acid showing crystallographic numbering scheme

Accordingly the isopropylidene protecting group was removed from **1** by reaction with aqueous trifluoroacetic acid to give the azido triol **6**, m.p. 102-104 °C, $[\alpha]_D^{20}$ +186.7 (*c*, 1.05 in MeOH) in 97% yield. Hydrogenation of **6** in ethanol in the presence of palladium black afforded the aminolactone **7** [88% yield] which on reaction with aqueous triethylamine and purification by ion exchange chromatography gave a mixture of *two* amino acids in a ratio of 8:1 and a combined yield of 86%. The major component, purified by crystallisation from water, was shown to be the anticipated direct ring opening product **11**,[2] the relative and absolute configurations of which [Figure 1] were firmly established by X-ray crystallographic analysis.[3] It has not yet been possible to obtain a pure sample of the minor amino acid component; the ^1H NMR data of a mixture of the two amino acids shows the structure of the minor product is highly symmetrical and may be consistent with **10**.

Removal of the ketal protecting group from **3** by aqueous trifluoroacetic acid afforded the unprotected azide **9**, m.p. >170 °C (dec), $[\alpha]_D^{20}$ +61.3 (*c*, 1.05 in MeOH) in 91% yield which on hydrogenation gave the aminolactone **8**. Reaction of **8** with aqueous sodium hydroxide gave a mixture of two amino acids in a ratio of 6:1 and a combined yield of 59%. The minor product was the optically inactive acid **5**, arising from direct

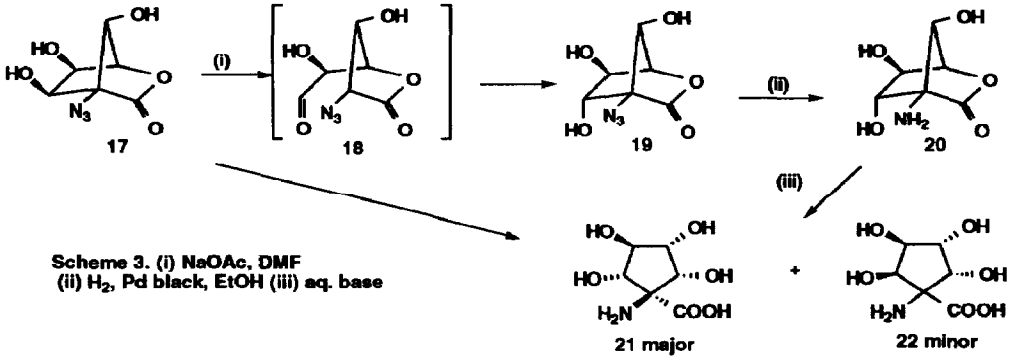


Scheme 2. Ring opening and aldol equilibrations of amino lactones 7 and 8

ring opening; this is direct contrast to **5** being the sole isolated product from opening of the protected azides **1** and **3**. The major amino acid component was **12**,[4] the enantiomer of **11** which was the major ring opening

product of **7**. The enantiomeric relationship between **11** and **12** was established by identical ^{1}H and ^{13}C NMR spectra of the two compounds and by the data in the footnotes in relation to the specific rotation of the materials at five different wavelengths.[5] A plausible explanation for these transformation is proposed in Scheme 2. The major product **11** from the ring opening of **7** by an oxygen nucleophile arises by attack from the least hindered *exo* face of the bicycloheptane framework with a minor product from a prior aldol equilibration *via* cleavage of the bond between the bridgehead position and the two carbon diol bridge to give **13** which recloses to **14** and then opens to **10**. In contrast, ring opening by attack on the *exo* face of **8**, hindered relative to **7** by the *syn* hydroxyl group, is a minor pathway in comparison to reverse aldolisation of **8** to give **15** followed by an aldol reaction to give **16** and finally ring opening to **12**.

It is generally the case, for good kinetic reasons,[6] that very highly substituted cyclopentanes cannot be made by intramolecular aldol-type condensations.[7] This chemistry demonstrates that there are circumstances where such closures can be efficient kinetically; the fact that the majority of the products arise from ring opening of the bicyclic structures, rather than diversion of the monocyclic intermediates indicates that such frameworks are likely to prove to be useful synthetic intermediates.



Scheme 3. (i) NaOAc, DMF (ii) H_2, Pd black, EtOH (iii) aq. base

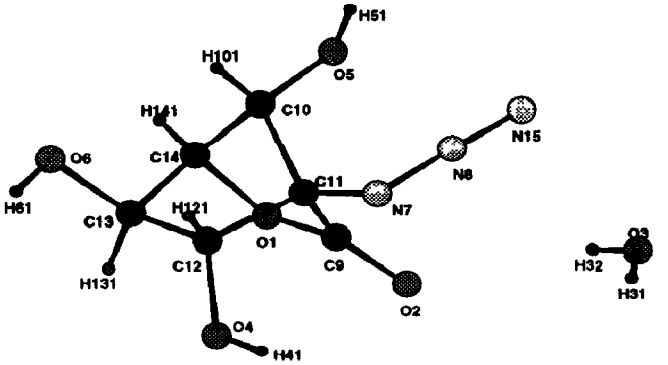
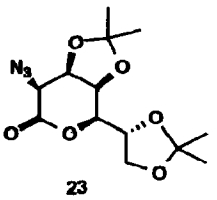


Figure 2. X-ray Molecular Structure of **19**, (1R,4R,5S,6R,7R)-1-Azido-5,6,7-trihydroxy-2-oxabicyclo[2.2.1]heptan-3-one with crystallographic numbering scheme

In earlier papers in these studies,[1] the closure to bicycloheptanone framework from δ-lactones with a 1 carbon aldehyde fragment has been firmly demonstrated. The observations in Scheme 2 indicate that such a closure should be possible from a γ-lactone with a two carbon side chain bearing the aldehyde. Thus the readily available azidolactone **17**[1] was treated with sodium acetate in dimethylformamide to form an isomeric azidolactone **19**, m.p. 143-144°C, $[\alpha]_D^{20}$ +25.3 (*c*, 1.0 in CH_3OH), in 94% yield,

based on unrecovered starting material; the structure of **19** was confirmed by X-ray crystallographic analysis [Figure 2], clearly demonstrating the isomerisation of *cis* to *trans* diol in the 2 carbon bridge. Hydrogenation of the azide **19** to the amine **20**, followed by opening of the lactone ring with aqueous triethylamine gave a mixture of the known[1] amino acid **22** as a minor product, together with a new amino acid **21** as the major product in a combined yield of 95%. Prior protection of the hydroxyl groups in **19** before reduction and ring opening allows **21**[8] to obtained as a single stereoisomer.[9]

The work in this and the preceding[1] paper illustrates the remarkable ability of the azidolactone **23** as a divergent intermediate for the synthesis of highly functionalised cyclopentane α-amino acids. From unprotected bicyclic lactones, which may be formed in a controlled way, the new amino acids **11, 12, 21** and **10** are described [although the final unambiguous characterisation of **10** remains to be completed]; the previous paper[1] reports the synthesis of **22** and **5** from the same starting material.



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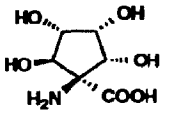

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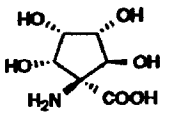

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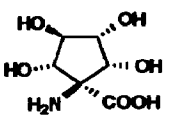

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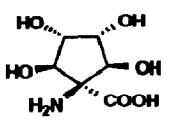

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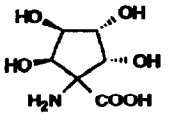

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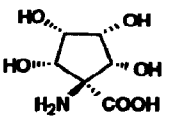

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In summary, the unexpected stability of the bicyclic systems and the subtlety of the balance between kinetic and thermodynamic stabilities of these materials provides practical and easy access to a range of complex α,α-amino acids; this work has implications for the future synthesis of complex cyclopentane derivatives.[10,11]

REFERENCES

[1]Fairbanks, A. J., Hui, A, Skead, B. M., Lilley, P.M. de Q., Lamont, R. B., Storer, R., Saunders, J., Watkin, D. J., Fleet, G. W. J., preceding paper and references therein.

[2]Selected data for amino acid **11**: m.p. >230 °C (dec.); $[\alpha]^{25}$ (*c*, 0.75 in H_2O): +3.7 (589), +2.9 (578), +3.2 (546), +6.1 (436), +10.0 (365); ν_{max} (KBr) 3400-3300 (br, OH, NH) cm^{-1} ; δ_H (D_2O) 3.85 (1H, dd, J 4.0 Hz, J' 8.6 Hz), 3.89 (1H, m), 4.21 (1H, d, J 4.5 Hz), 4.41 (1H, d, J' 8.6 Hz); δ_C (D_2O) 69.0 (s, C-1), 72.1, 73.4, 76.4, 77.3 (4 x d, C-2, C-3, C-4, C-5), 173.8 (s, C-6)

[3]Atomic coordinates for the amino acid **11** and the azidolactone **19** are available on request from the Cambridge Crystallographic Data Centre, University Chemistry Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used for the compounds elsewhere in the text. Any requests should be accompanied by the full literature citation for this paper.

[4]Selected data for amino acid **12**: identical to **11** save in the specific rotation at the following wavelengths: $[\alpha]^{25}$ (*c*, 0.75 in H_2O): -4.4 (589), -3.5 (578), -4.0 (546), -6.5 (436), -9.6 (365)

[5]The enantiomeric relationship of **11** and **12** is confirmed by CD studies which will be reported in the full paper.

[6]Baldwin, J. E., Lusch, M. J., *Tetrahedron*, 1982, **38**, 2939; J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

[7]Ferrier, R. J., and Haines, S. R., *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1689.

[8]Selected data for amino acid **21**: δ_H (D_2O, 500 MHz): 3.94 (1H, dd, *J* 8.0 Hz, *J*'3.8 Hz), 3.95 (1H, d, *J* 7.4 Hz), 4.27 (1H, d, *J* 8.0 Hz), 4.33 (1H, dd, *J* 7.4 Hz, *J* 3.8 Hz); δ_C (D_2O, 125 MHz): 72.7 (s, C-1), 71.4, 75.2, 77.8, 83.0 (4 x d, C-2, C-3, C-4, C-5), 170.7 (s, C-6).

[9]The protection and ring opening of azidotriols will be reported in due course.

[10]Ferrier, R. J., Middleton, S., *Chem. Rev.*, 1993, **93**, 2779.

[11]Fully funded 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)