Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1855–1859

TETRAHEDRON: *ASYMMETRY*

3-Azidotetrahydrofuran-2-carboxylates: monomers for five-ring templated β-amino acid foldamers?

Mark P. Watterson,[a] Lea Pickering,[a] Martin D. Smith,[a] Sarah J. Hudson,[a] Paul R. Marsh,[a] Jacqueline E. Mordaunt,[c] David J. Watkin,[b] Christopher J. Newman [b] and George W. J. Fleet [a,*]

[a]*Dyson Perrins Laboratory, Oxford Centre for Molecular Sciences, South Parks Road, Oxford, OX1 3QY, UK*
[b]*Chemical Crystallography Department, Oxford University, Parks Road, Oxford, OX1 3PD, UK*
[c]*GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK*

Received 29 April 1999; accepted 20 May 1999

Abstract

Four diastereomeric methyl 3-azidotetrahydrofuran-2-carboxylates were prepared from diacetone glucose as precursors for the synthesis of β-amino acid oligomers with secondary structure.

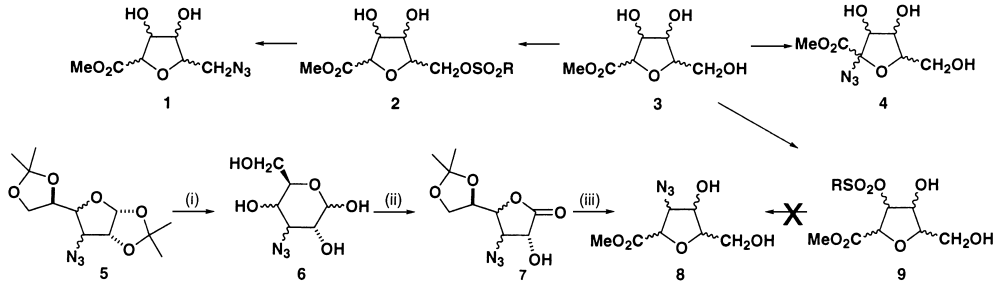
Conformationally constrained amino acids provide access to short sequences of peptide mimetics with secondary structure and thus may generate new opportunities for the design of antagonists and agonists of specific protein–protein interactions.[1] Oligomers of β-amino acids are more prone than those derived from α-amino acids to possess conformational rigidity.[2] There has recently been much interest in the synthesis of monomers — and the structures of oligomers — containing a β-amino acid moiety.[3] For example, Gellman has shown that oligomers containing only six β-amino acid residues — some of which were a *trans*-2-aminocyclohexane carboxylic acid — can form stable helices in aqueous solutions.[4] Other structural units which have β-amino acid equivalents in rigid ring templates are likely to induce secondary structure in relatively short sequences.[5]

Oligomers derived from different diastereomers of 5-azidomethyl carboxylates **1** form both β-turns[6] and α-helices;[7] one diastereomer of **1** was shown by Chakraborty to be an isostere for Gly-Gly in enkephalins, producing materials with much the same biological activity as that of the natural products.[8] The synthesis of **1** depends on the efficient acid and base catalysed conversions of 2-*O*-trifluoromethanesulfonates (triflates) of γ- and δ-lactones to highly substituted tetrahydrofuran-2-carboxylates (THFC) **3** (Scheme 1).[9] Esterification of **3** at C-5 to afford sulfonates **2** and subsequent reaction with sodium azide allows a general approach to **1**. Radical bromination of **3**, followed by treatment of the resulting α-bromoester with sodium azide, permits the generation of α-azidoesters **4** which also provides the opportunity to generate peptidomimetics with secondary structure.[10] One

* Corresponding author.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00205-0

strategy for the synthesis of the diastereomeric β-azidoesters **8** is the activation of the C-3 hydroxyl group in **3** to give **9**; although the 3-sulfonylesters **9** were readily formed — and in some cases could be isolated — all attempts to induce substitution of the leaving group with an azide ion resulted in elimination reactions; in fact sodium azide in DMF was among the most efficient bases to induce elimination to the corresponding α,β-unsaturated esters.[11] Accordingly, a different approach to the synthesis of the azidoesters **8** is required in which the azide is introduced into the sugar prior to the formation of the THF ring.

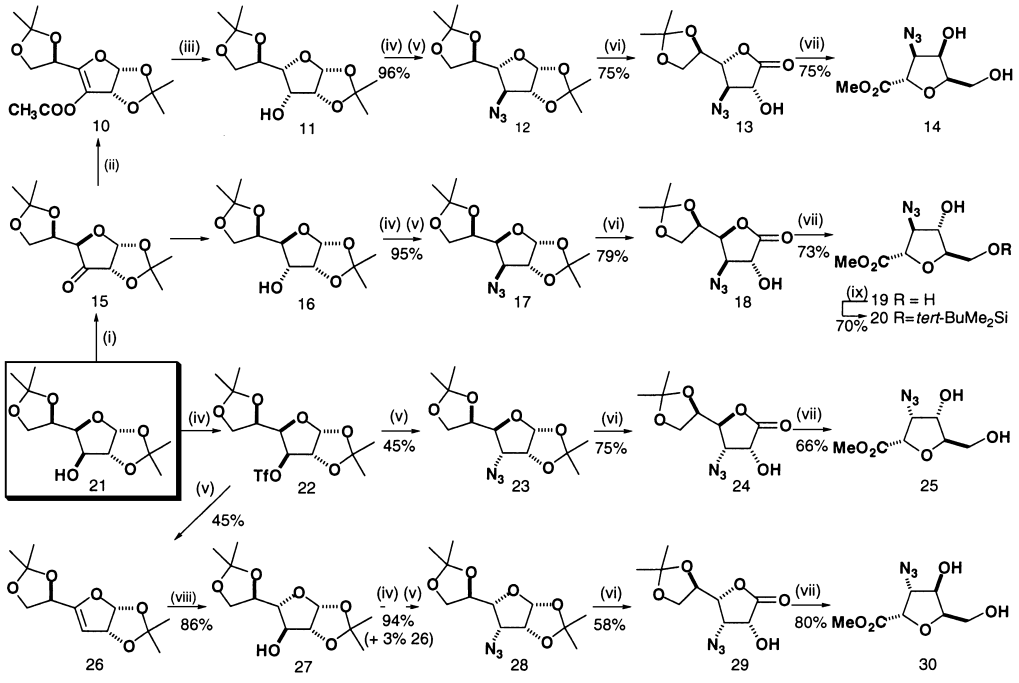


Scheme 1. (i) Aq. CF_3COOH; (ii) Br_2, $BaCO_3$, H_2O; then Me_2CO, CSA; (iii) Tf_2O, pyridine, CH_2Cl_2; then HCl, MeOH

This paper reports the synthesis of four diastereomeric β-azidoTHFC esters **8** from the four diastereomeric diacetone azides **5**, all of which were prepared from diacetone glucose **21** (Scheme 2). In the case of each diastereomer of **5**, hydrolysis gave the corresponding free 3-azidohexose **6**. Oxidation of each of the diastereomers of **6** with bromine water gave mixtures of lactones and open chain acids, but direct protection of these mixtures allowed the isolation of the protected azidolactones **7**. Esterification of the remaining free hydroxyl group in **7** with triflic anhydride, followed by reaction with hydrogen chloride in methanol, formed the target β-azidoesters **8**; this transformation involved removal of the acetonide protecting group, methanolysis of the lactone to give the open chain methyl ester, and attack by the free C-5 OH group at the C-2 triflate to give S_N2 ring closure with inversion at C-2 producing the β-azidoTHFC **8**.

Thus, oxidation of diacetone glucose **21** with PCC in dichloromethane in the presence of molecular sieve gave the ketone **15** which with acetic anhydride in pyridine afforded the enol acetate **10** (Scheme 2). Hydrogenation of the enol acetate in the presence of palladium black in ethyl acetate, followed by ester exchange, gave the *gulo*-alcohol **11**, epimeric with **21** at both C-3 and C-4, as previously described.[12] Triflation of the free hydroxyl group in **11**, followed by azide displacement, gave the azide **12**[13] in 96% yield. Removal of the protecting groups in **12** by aqueous trifluoroacetic acid, followed by oxidation of the free sugar with bromine and treatment of the residue of the reaction with acetone in the presence of camphorsulfonic acid, afforded the *galactono*-azide **13**,[14] oil, $[\alpha]_D^{25}$ −68.2 (*c*, 1.00 in $CHCl_3$), in an overall yield of 75%. Further reaction of the lactone **13** with triflic anhydride in dichloromethane in the presence of pyridine, followed by treatment with hydrogen chloride in methanol, gave the azidotalonate **14**[15] in 75% yield. Reduction of the ketone **11** with sodium borohydride gave the *allo*-alcohol **16** which was converted into the azide **17** in 95% yield, as previously described.[16] Hydrolysis of **17**, followed by oxidation and acetonation, afforded the *glucono*-azide **18**, oil, $[\alpha]_D^{23}$ +71.1 (*c*, 1.11 in chloroform), in an overall yield of 79%. Triflation of **18** with subsequent acidic methanolysis gave the azidomannonate **19**,[17] epimeric at C-4 with **14**, in 73% yield. The structure of **19** was unequivocally established by X-ray crystallographic analysis[18] of the silyl ether **20**.[19]

For the synthesis of the two other diastereomeric azidoTHFC esters **25** and **30**, diacetone glucose **21** was converted to the triflate **22**; treatment of **22** with sodium azide in DMF[20] gave a 1:1 mixture of the vinyl ether **26** and the *allo*-azide **23** in a combined yield of 90%. Elaboration of **23** by hydrolysis,



Scheme 2. (i) PCC, CH_2Cl_2, molecular sieve; (ii) pyridine, Ac_2O; (iii) Pd black, H_2, EtOAc; then K_2CO_3 in MeOH; (iv) Tf_2O, pyridine, CH_2Cl_2; (v) NaN_3, DMF; (vi) aq. CF_3COOH; then Br_2, $BaCO_3$, H_2O; then Me_2CO,CSA; (vii) Tf_2O, pyridine, CH_2Cl_2; then HCl, MeOH; (viii) 9-BBN in THF; then H_2O_2, NaOH; (ix) TBDMSCl, imidazole, DMF

oxidation and acetonation afforded the *allono*-azide **24**, m.p. 176–177°C, $[\alpha]_D^{25}$ +110.5 (*c*, 1.08 in acetone), in 75% yield; triflation of **24** followed by acidic methanolysis gave the azidoaltronate **25**[21] in 66% yield. The structure of **25** was confirmed by X-ray crystallographic analysis.[18] Hydroboration of the alkene **26** with 9-borabicyclononane [9-BBN] in THF followed by oxidation with alkaline hydrogen peroxide gave the *galacto*-alcohol **27** in 86% yield, significantly higher than that obtained with borane in THF.[22] Triflation of **27** followed by reaction with sodium azide in DMF gave the previously unknown *gulo*-azide **28**, m.p. 86–87°C, $[\alpha]_D^{25}$ +146.5 (*c*, 1.05 in $CHCl_3$), in 94% yield [together with a small amount of the elimination product **26**]. The contrast in the ratio of elimination to substitution in this case in comparison to the reaction of the *gluco*-triflate **22** is noteworthy. The diacetonide **28** was elaborated to give the *gulono*-lactone **29**, m.p. 166–167°C, $[\alpha]_D^{24}$ +120.4 (*c*, 1.21 in acetone) [in 58% yield] and further to the azidoidonate **30**[23] [in 80% yield].

In summary, this paper validates a general approach to 3-azidoTHFC esters from 3-azidolactones. Studies on the synthesis and structures of oligomers derived from the two *cis*- **25** and **30** and the two *trans*- **14** and **19** β-amino acid monomers are currently in progress.

Acknowledgements

Support from BBSRC and EPSRC is acknowledged.

References

1. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789; Clerici, F.; Gelmi, M. L.; Pocar, D. *J. Org. Chem*. **1999**, *64*, 726; Hanessian, S.; Luo, X. H.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc*. **1998**, *120*, 8569; Gellman, S. H. *Curr. Opin. Chem. Biol*. **1998**, *2*, 717.
2. Gellman, S. H. *Acc. Chem. Res*. **1998**, *31*, 173.
3. Martin Vila, M.; Minguillon, C.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1998**, *9*, 4291; Gademann, K.; Jaun, B.; Seebach, D.; Perozzo, R.; Scapozza, L.; Folkers, G. *Helv. Chim. Acta* **1999**, *82*, 1; Daura, X.; Gademann, K.; Jaun, B.; Seebach, D.; vanGunsteren, W. F.; Mark, A. E. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 236; Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141; Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1998**, *120*, 10555; Applequist, J.; Bode, K. A.; Appella, D. H.; Christianson, L. A.; Gellman, S. H. *J. Am. Chem. Soc*. **1998**, *120*, 4891.
4. Appella, D. H.; Barchi, J. J.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1999**, *121*, 1806.
5. Smith, M. D.; Long, D. D.; Claridge, T. D. W.; Marquess, D. G.; Fleet, G. W. J. *Chem. Commun*. **1998**, 2039; Smith, M. D.; Long, D. D.; Martín, A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett*. **1999**, *40*, 2191; Long, D. D.; Stetz, R. J. E.; Nash, R. J.; Marquess, D. G.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 901.
6. Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet G. W. J. *Chem. Commun*. **1998**, 2041; Long, D. D.; Smith, M. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett*. **1998**, *39*, 9293; Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge T. D. W.; Fleet, G. W. J. *Tetrahedron Lett*. **1999**, *40*, 2195.
7. Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett*. **1999**, *40*, 2199.
8. Chakraborty, T. K.; Jayaprakash, S.; Diwan, P. V.; Nagaraj, R.; Jampani, S. R. B.; Kunwar A. C. *J. Am. Chem. Soc*. **1998**, *120*, 12962.
9. Wheatley, J. R.; Bichard, C. J. F.; Mantell, S. J.; Son, J. C.; Hughes, D. J.; Fleet, G. W. J.; Brown, D. *J. Chem. Soc., Chem. Commun*. **1993**, 1065; Choi, S. S.; Myerscough, P. M.; Fairbanks, A. J.; Skead, B. M.; Bichard, C. J. F.; Mantell, S. J.; Fleet, G. W. J.; Saunders, J. D.; Brown, D. *J. Chem. Soc., Chem. Commun*. **1992**, 1605; Bichard, C. J. F.; Brandstetter, T. W.; Estevez, J. C.; Fleet, G. W. J.; Hughes, D. J.; Wheatley, J. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2151.
10. Smith, M. D.; Long, D. D.; Martín, A.; Campbell, N.; Blériot, Y.; Fleet, G. W. J. *Synlett*, in press, and references cited therein.
11. Watterson, M. P.; Smith, M. D. unpublished results.
12. Legler, G.; Pohl, S. *Carbohydr. Res*. **1986**, *155*, 119.
13. Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res*. **1994**, *251*, 33.
14. Satisfactory spectroscopic and microanalytical or HRMS data was obtained for all new compounds reported.
15. Data for azidotalonate **14**: colourless oil; $[\alpha]_D^{25}$ +72.8 (*c*, 0.25 in $CHCl_3$); ν_{max} (film) 3369 (OH), 2114 (N_3), 1742 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 3.83 (3H, s, CO_2CH_3), 3.92 (1H, dd, $J_{6',5}$ 4.1, $J_{6',6}$ 12.3, H-6′), 3.97 (1H, dd, $J_{6,5}$ 4.6, $J_{6',6}$ 12.3, H-6), 4.09 (1H, dd, $J_{3,2}$ 7.3, $J_{3,4}$ 4.7, H-3), 4.22 (1H, app-q, J 4.3, H-5), 4.52 (1H, app-t, J 4.4, H-4), 4.57 (1H, d, $J_{2,3}$ 7.3, H-2); δ_C ($CDCl_3$, 50.3 MHz) 52.8 (q, CO_2CH_3), 61.0 (t, C-6), 66.2, 73.3, 78.0, 81.3 (4×d, C-2, C-3, C-4, C-5), 171 (s, C-1).
16. Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095.
17. Data for azidomannonate **19**: yellow oil; $[\alpha]_D^{24}$ +75.3 (*c*, 1.01 in methanol); ν_{max} (film) 3400 (OH), 2113 (N_3), 1744 (C=O) cm^{-1}; δ_H (d_4-methanol, 400 MHz) 3.63 (1H, dd, $J_{6',5}$ 4.7, $J_{6',6}$ 12.2, H-6′), 3.75 (1H, dd, $J_{6,5}$ 3.5, $J_{6,6'}$ 12.2, H-6), 3.81 (3H, s, CO_2CH_3), 3.92–3.96 (1H, m, H-5), 4.07 (1H, app-t, J 5.8, H-4), 4.15 (1H, app-t, J 5.6, H-3), 4.30 (1H, d, $J_{2,3}$ 5.6, H-2); δ_C ($CDCl_3$, 50.3 MHz) 52.9 (q, CO_2CH_3), 61.3 (t, C-6), 69.9, 75.4, 79.2, 84.4 (4×d, C-2, C-3, C-4, C-5), 171.3 (s, C-1).
18. The X-ray crystal structures of **20** and **25** will be reported in a full paper.
19. Data for the silyl ether **20**: m.p. 73–75°C (ethyl acetate); $[\alpha]_D^{24}$ +39.7 (*c*, 1.00 in chloroform); ν_{max} (film) 3463 (OH), 2105 (N_3), 1742 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.09 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 2.55 (1H, s, br, OH), 3.72 (1H, dd, $J_{6',5}$ 6.3, $J_{6',6}$ 10.6, H-6′), 3.83 (3H, s, CO_2CH_3), 3.86 (1H, dd, $J_{6,5}$ 4.2, $J_{6,6'}$ 10.6, H-6), 4.03 (1H, app-dt, J 4.2, J 6.3, H-5), 4.15 (1H, app-t, J 5.6, H-3), 4.22 (1H, app-t, J 5.6, H-4), 4.39 (1H, d, $J_{2,3}$ 5.6, H-2); δ_C ($CDCl_3$, 50.3 MHz) −5.7 (q, $Si(CH_3)_2$), 18.1 (s, $SiC(CH_3)_3$), 25.7 (q, $SiC(CH_3)_3$), 52.7 (q, CO_2CH_3), 62.8 (t, C-6), 69.9, 76.9, 79.6, 84.3 (4×d, C-2, C-3, C-4, C-5), 171.6 (s, C-1).
20. Daley, L.; Monneret, C.; Gautier, C.; Roger, P. *Tetrahedron Lett*. **1992**, *33*, 3749.

21. Data for azidoaltronate **25**: m.p. 94–95°C (toluene/ethyl acetate); $[\alpha]_D^{25}$ +95.2 (*c*, 0.88 in $CHCl_3$); ν_{max} (KBr disc) 3489, 3370 (OH), 2121 (N_3), 1757 (C=O) cm^{-1}; δ_H (CD_3OD, 400 MHz) 3.58 (1H, dd, $J_{6',5}$ 3.7, $J_{6',6}$ 12.4, H-6′), 3.78 (3H, s, CO_2CH_3), 3.81 (1H, dd, $J_{6,5}$ 2.4, $J_{6,6'}$ 12.4, H-6), 3.90 (1H, app-dt, J 3.0, $J_{5,4}$ 8.6, H-5), 4.36 (1H, app-t, J 4.8, H-3), 4.44 (1H, dd, $J_{4,3}$ 5.1, $J_{4,5}$ 8.6, H-4), 4.70 (1H, d, $J_{2,3}$ 4.6, H-2); δ_C (CD_3OD, 50.3 MHz) 52.7 (q, CO_2CH_3), 61.8 (t, C-6), 67.0, 73.2, 79.1, 83.7 (4×d, C-2, C-3, C-4, C-5), 171.6 (s, C-1).
22. Paulsen, H.; Behre, H. *Carbohydr. Res*. **1966**, *2*, 80.
23. Data for azidoidonate **30**: oil; $[\alpha]_D^{24}$ +50.9 (*c*, 1.05 in $CHCl_3$); ν_{max} (film) 3369 (OH), 2116 (N_3), 1749 (C=O) cm^{-1}; δ_H (CD_3OD, 400 MHz) 3.72 (1H, dd, $J_{6',5}$ 5.8, $J_{6',6}$ 11.6, H-6′), 3.77 (1H, dd, $J_{6,5}$ 5.4, $J_{6,6'}$ 11.6, H-6), 3.78 (3H, s, CO_2CH_3), 4.15 (1H, app-dt, J 5.5, $J_{5,4}$ 3.7, H-5), 4.30–4.32 (2H, m, H-3, H-4), 4.84 (1H, d, $J_{2,3}$ 4.8, H-2); δ_C (CD_3OD, 50.3 MHz) 52.6 (q, CO_2CH_3), 61.1 (t, C-6), 70.9, 76.1, 79.6, 83.4 (4×d, C-2, C-3, C-4, C-5), 171.9 (s, C-1).