Pergamon

Tetrahedron Letters 40 (1999) 2191–2194

TETRAHEDRON LETTERS

Absence of Secondary Structure in a Carbopeptoid Tetramer of a *trans*-5-Aminomethyl-Tetrahydrofuran-2-carboxylate.

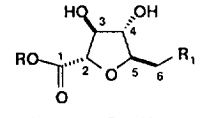
Martin D. Smith,[a] Daniel D. Long,[a] Angeles Martín,[a] Daniel G. Marquess,[b,c] Timothy D. W. Claridge[a] and George W. J. Fleet[a,*]

[a]Dyson Perrins Laboratory, Oxford Center for Molecular Sciences, South Parks Road, Oxford, OX1 3QY, UK.
[b]GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.
[c]Advanced Medicine Inc., 270 Littlefield Avenue, Suite B, South San Francisco CA 94080, USA.

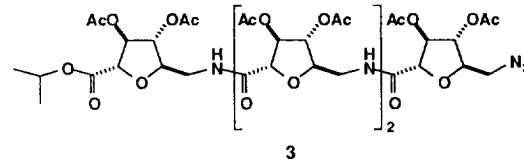
Received 11 December 1998; accepted 7 January 1999

Abstract: Whereas trimers and tetramers of β-*C*-D-arabinofuranosyl carbohydrate amino acids adopt well defined conformations based around a repeating β-turn like structure, stabilised by (i, i-2) inter-residue hydrogen bonds, there is no indication of any secondary structure in the tetramer of the epimeric α-*C*-D-arabinofuranosyl carbohydrate amino acid, where the C-2 and C-5 substituents of the tetrahydrofuran ring are *trans* to each other.

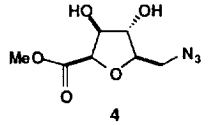
The exquisite specificity of recognition and catalysis exhibited by enzymes are enviable properties for any molecule to possess. These attributes emerge through folding and self organisation of flexible chains into specific and well defined conformations – sometimes bringing covalently distant components into close spatial proximity. Attempts to mimic the structure of natural polymers are varied,[1] and unnatural oligomeric peptides[2] which display secondary structure in relatively short chains, have been investigated intensely.[3] Polymers which have a tendency to adopt a specific compact conformation have been termed 'foldamers'.[4] The first step in the creation of artificial protein-like structures (which might display specific tertiary structure) is the identification of novel scaffolds[5] which possess an inherent propensity to generate secondary structural elements. This has proven to be a fruitful approach resulting in the synthesis of a range of molecules exhibiting helical[6] and other secondary structures.[7]



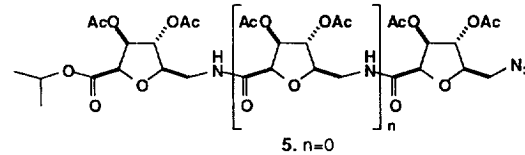
1. $R_1 = N_3$, R = H
2. $R_1 = NH_2$, R=isopropyl



3



4



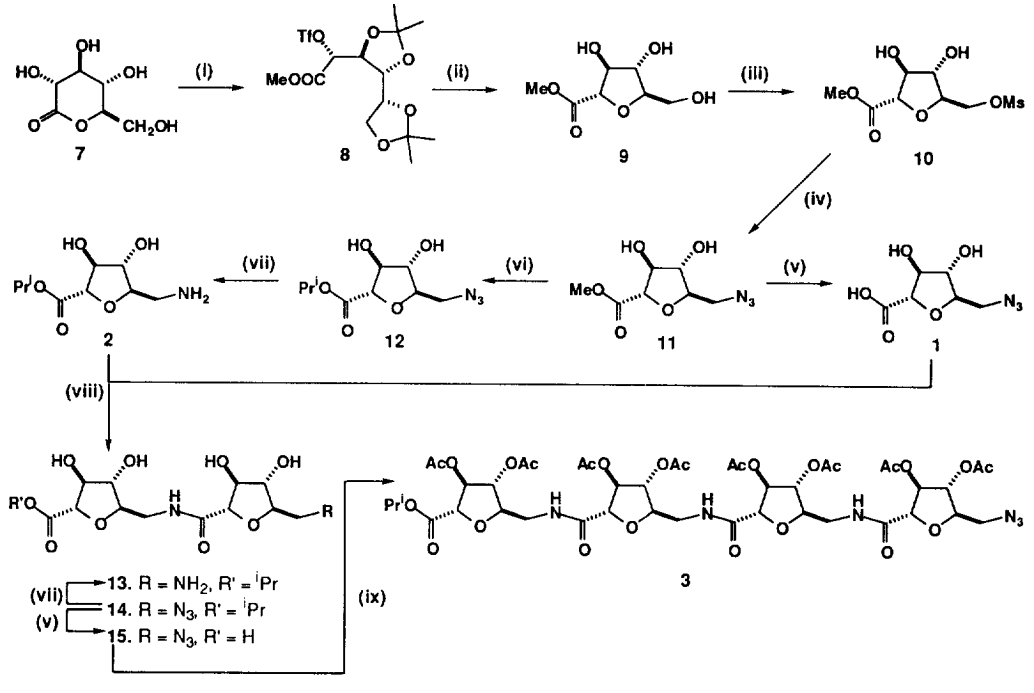
5. n=0
6. n=2

Carbohydrates bearing both an amino and a carboxylic acid functionality have been proposed as combinatorial building blocks[8] and peptidomimetics;[9] they are found as components of both natural products[10] and potent inhibitors of sugar processing enzymes.[11] Exploitation of the rigidity and diversity of the sugar backbone should permit subtle modification and even a rational design for three dimensional conformation in oligomeric derivatives ('carbopeptoids').[12] However, access in short sequences to a flexible range of carbohydrate-based amino acids has thus far proved elusive and has hampered such objectives; a wide range of tetrahydrofuran azidoacids are available from carbohydrate lactones and may provide a family of novel combinatorial building blocks as well as clues to the design of short sequences exhibiting secondary structure.

PII: S0040-4039(99)00109-4

Oligomers **6** derived from a *cis*-5-aminomethyl-tetrahydrofuran-2-carboxylate **4** can exhibit secondary structure in chains as short as a trimer.[13] In order to investigate the effects of structure variation in this framework, this paper reports the synthesis of the tetrameric C-2 epimer **3** in which the C-2 and C-5 substituents of the tetrahydrofuran ring are *trans* to each other. The inversion of this single stereocenter from **6** to **3** confers significant changes upon the solution state conformation such that in **3** no secondary structure is apparent.

The synthesis of the 2,5-*trans* carbopeptoid **3** is described in scheme 1. The open chain triflate **8** was synthesised from D-glucono-1,5-lactone **7** as previously described.[14] Treatment of the triflate **8** with methanolic hydrogen chloride gave exclusively the α-*C*-D-arabinofuranosyl carboxylate **9** $[\alpha]_D^{23}$ +47.2 (*c*, 1.0 in MeOH) in 90% yield *via* an S_N2-like closure of the C-5 hydroxyl onto C-2 with inversion of configuration.[15] The triol **9** underwent a selective esterification with methanesulphonyl chloride in pyridine in the presence of 4-dimethylaminopyridine at -20°C to give the primary mesylate **10** $[\alpha]_D^{21}$ +41.7 (*c*, 1.01 in MeOH), m.p. 74-75°C, in 72% yield which upon treatment with sodium azide in *N*,*N*-dimethylformamide (DMF) at 65°C afforded the azido ester **11** in 98% yield $[\alpha]_D^{21}$ +70.2 (*c*, 0.88 in MeOH).[16]



Scheme 1. (i) ref 3. (ii) 1%HCl in MeOH, RT (iii) MsCl, py, DMAP (iv) NaN_3, DMF, 65°C (v) NaOH (aq), dioxane (vi) $(CH_3)_2CHOH$, K_2CO_3 (vii) H_2, Pd, $(CH_3)_2CHOH$ (viii) EDCI, HOBt, $(iPr)_2NEt$, 1 eq. of **1** (ix) EDCI, HOBt, $(iPr)_2NEt$, 1 eq. of **13** then Ac_2O.

Attempts to reduce the C-6 azide of **11** under standard hydrogenation conditions led to complex mixtures of products, probably arising from intermolecular condensations; a less reactive ester is required to enable isolation of the C-6 amine. Thus, transesterification of the methyl ester **11** to the more hindered isopropyl ester **12** $[\alpha]_D^{23}$ +58.6 (*c*, 1.0 in MeOH), m.p. 48-52°C, was effected by heating at 70°C in isopropanol in the presence of potassium carbonate (84% yield). Subsequent hydrogenation of the isopropyl azide **12** in isopropanol in the presence of palladium black allowed isolation of the polar amino ester **2** which was used without further purification. Hydrolysis of the ester functionality in **11** with aqueous sodium hydroxide in dioxane and purification by ion exchange chromatography gave access to the acid **1** which was coupled to the 6-amino component **2** under standard conditions with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) in DMF in the presence of diisopropylethylamine. This gave the unprotected dimer **14** (74% yield from the azide **12**) $[\alpha]_D^{23}$ +46.6 (*c*, 0.5

in MeOH), m.p. 142-143°C, which is isolable by standard chromatographic techniques. Protection of the backbone hydroxyl groups is unnecessary during these coupling reactions. An iterative approach was adopted for the synthesis of the tetrameric carbopeptoid **3**; thus the dimer **14** was reduced by hydrogenation in isopropanol in the presence of palladium black to afford the *N*-terminal amine **13**. Treatment of the dimer **14** with aqueous sodium hydroxide in dioxane gave the acid **15** which could be coupled to the *N*-terminal dimeric amine **13** with EDCI and HOBt in DMF in the presence of diisopropylethylamine. Treatment of the reaction mixture with acetic anhydride in pyridine facilitated isolation of the peracetylated tetramer **3** $[\alpha]_D^{24}$ +58.6 (*c*, 0.5 in $CHCl_3$) in 77% yield from the azide **14**.

The solution structure of the tetramer **3** was investigated by NMR spectroscopy. Partial proton spectra of the *cis* **6** and *trans* **3** tetramers are depicted in figure 1 for comparison. The proton spectrum of the *cis* tetramer **6** (lower plot) in $CDCl_3$ is remarkably well dispersed, despite the repeating monomer units. The amide proton region of *cis* **6** is particularly distinctive; two protons display high frequency shifts whereas the third resonates at a considerably lower chemical shift. It has previously been shown that the two protons above 8 ppm (NH^C and NH^D)[17] are involved in intramolecular hydrogen bonding interactions (NH^i, CO^{i-2}) in $CDCl_3$ solutions, whereas the third (NH^B) is solvent exposed. These hydrogen bonds stabilise a novel repeating β-turn type secondary structure which gives rise to the significant shift dispersion.

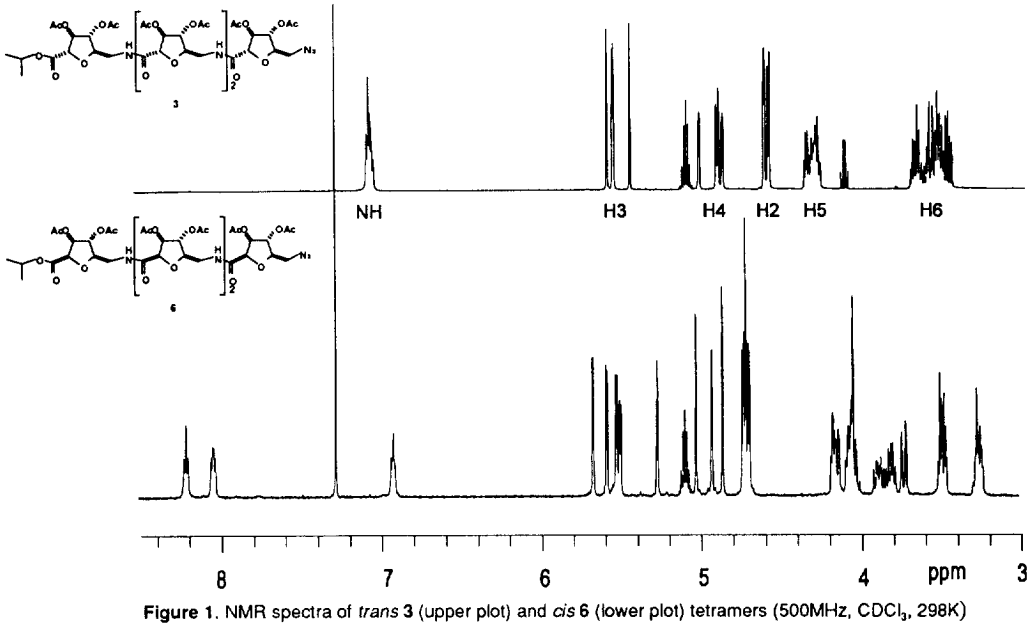


Figure 1. NMR spectra of *trans* **3** (upper plot) and *cis* **6** (lower plot) tetramers (500MHz, $CDCl_3$, 298K)

In sharp contrast, the proton spectrum of the *trans* isomer **3** demonstrates very little shift distribution, with all protons clustered together according to their positions within the monomer units. Outlying resonances from these clusters can be attributed to chemical differences at the termini, in particular the presence of the *C*-terminal ester functionality. The distinct lack of dispersion and similar chemical shifts for the amide protons indicates an absence of hydrogen bonding interactions. These amide proton shifts are similar to that observed for the *cis* dimer **5** in $CDCl_3$ (7.18 ppm) which itself does not participate in internal hydrogen bonding. Overall, the low dispersion observed throughout the spectrum is generally suggestive of a lack of stable secondary structure. The 2,5-*trans* disposition of the groups across the tetrahydrofuran ring in **3** would not provide the optimum geometry for the formation of the hydrogen bonded turn-type structure observed for the *cis* isomer **6** but may not necessarily prevent the formation of alternative secondary structures; however, a larger oligomer than a tetramer is clearly necessary for this. In the following paper the synthesis[18] of three further stereoisomeric tetramers of **3**, with both *cis* and *trans* arrangements of the 2,5-substituents and in all of

which a *cis*-diol unit is protected as a ketal, is described; all three of these tetrameric carbopeptoids provide preliminary indications of the presence of secondary structural characteristics.[19,20]

References.

[1] Soth, M. J., Nowick, J. S., *Curr. Opin. Chem. Biol.*, **1997**, *1*, 120.

[2] Armand, P., Kirshenbaum, K., Goldsmith, R. A., FarrJones, S., Barron, A. E., Truong, K. T. V., Dill, K. A., Mierke, D. F., Cohen, F. E., Zuckermann, R. N., Bradley, E. K., *Proc. Natl. Acad. Sci. U. S. A.*, **1998**, *95*, 4309.

[3] Smith, M. D., Claridge, T. D. W., Tranter, G. E., Sansom, M. S. P., Fleet, G. W. J., *J. Chem. Soc., Chem. Commun.*, **1998**, 2041; Appella, D. W., Christianson, L. A., Klein, D. A., Powell, D. R., Huang, X., Barchi, J. J., Gellman, S. H., *Nature*, **1997**, *387*, 381; Seebach, D., Matthews, J. L., *J. Chem. Soc., Chem. Commun.*, **1997**, 2015; Nelson, J. C., Saver, J. G., Moore, J. S., Wolynes, P. G., *Science*, **1997**, *277*, 1793.

[4] Gellmann, S. H., *Acc. Chem. Res.*, **1998**, *31*, 173.

[5] Smith, M. D., Long, D. D., Marquess, D. G., Claridge, T. D. W., Fleet, G. W. J., *J. Chem. Soc., Chem. Commun.*, **1998**, 2039.

[6] Seebach, D., Abele, S., Gademann, K., Guichard, G., Hintermann, T., Jaun, B., Matthews, J. L., Schreiber, J. V., *Helv. Chim. Acta*, **1998**, *81*, 932; Hamuro, Y,. Geig, S. J, Hamilton, A. D., *J. Am. Chem. Soc.*, **1997**, *119*, 10587; Christianson, L. A., Karla, I. L., Powell, D. R., Gellman, S. H., *J. Am. Chem. Soc.*, **1996**, *118*, 13071; Hanessian, S., Luo, X. H., Schaum, R., Michnick, S., *J. Am. Chem. Soc.*, **1998**, *120*, 8569.

[7] Szabo, L, Smith, B. L., McReynolds, K. D., Parill, A. L., Morris, E. R., Gervay, J., *J. Org. Chem.*, **1998**, *63*, 1074; Nowick, J. S., Mahrus, S., Smith, E. M., Ziller, J. W., *J. Am. Chem. Soc.*, **1996**, *118*, 1066; Nowick, J. S., Smith, E. M., Pairish, M., *Chem. Soc. Rev.*, **1996**, *26*, 401. Lokey, R. S., Iverson, B. L., *Nature*, **1995**, *375*, 303.

[8] McDevitt, J. P., Lansbury, P. T., *J. Am. Chem. Soc.*, **1996**, *118*, 3818; Sofia, M. J., Hunter, R., Chan, T. Y., Vaughn, A., Dulina, R., Wang, H., Gange, D., *J. Org. Chem.*, **1998**, *63*, 2802.

[9] von Roedern, E. G., Lohof E., Hessler, G., Hoffmann, M., Kessler, H., *J. Am. Chem. Soc.*, **1996**, *118*, 10156; von Roedern, E. G., Kessler, H., *Angew. Chem. Int. Ed. Engl.*, **1994**, *334*, 687; Poitout, L., le Merrer, Y., Depazay, J.-C., *Tetrahedron Lett.*, **1995**, *36*, 6887.

[10] Nakajima, M., Itoi, K., Takamatsu, Y., Kinoshita, T., Okazaki, T., Kawakubo, K., Shindou, M., Honma, T., Tohjigamori, M., Hancishi, T., *J. Antibiot.*, **1991**, *44*, 293.

[11] Bichard, C. J. F., Mitchell, E. P., Wormald, M. R., Watson, K. A., Johnson, L. N., Zographos, S. E., Koutra, D. D., Oikonomakos, N. G., Fleet G. W. J., *Tetrahedron Lett.*, **1995**, *36*, 2145; Krülle, T. M., de la Fuente, C., Watson, K. A, Gregoriou, M., Johnson, L. N., Tsitsanou, K. E., Zographos, S. E., Oikonomakos, N. G., Fleet, G. W. J., *Synlett*, **1997**, 211.

[12] Nicolaou, K. C., Florke, H. M., Egan, G., Barth, T., Estevez, V. A., *Tetrahedron Lett.*, **1995**, *36*, 1775.

[13] Long, D. D., Smith, M. D., Marquess, D. G., Claridge, T. D. W., Fleet, G. W. J., *Tetrahedron Lett.*, **1998**, *39*, 9293.

[14] Csuk, R., Hugener, M., Vasella, A., *Helv. Chim. Acta.*, **1988**, *71*, 609; Regeling, H., de Rouville, E., Chittenden, G. J. F., *Recl. Trav. Chim. Pays-Bas*, **1987**, *106*, 461.

[15] Estevez, J. C., Fairbanks, A. J., Fleet, G. W. J., *Tetrahedron: Asymm.*, **1998**, *54*, 13591; 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., Brown, D., *J. Chem. Soc., Chem. Commun.*, **1992**, 1605.

[16] Selected data for methyl-2,5-anhydro-6-deoxy-6-azido-D-mannonate **11**: δ_H (500 MHz, D_2O) 3.52 (1H, dd, $J_{6,5}$ 6.4 , $J_{6,6'}$ 13.4, H-6), 3.64 (1H, dd, $J_{6',5}$ 3.8, $J_{6',6}$ 13.5, H-6'), 3.80 (3H, s, CO_2Me), 4.09 (1H, dd, $J_{4,3}$ 4.2, $J_{4,5}$ 4,7, H-4), 4.16 (1H, ddd, $J_{5,6'}$ 3.9, $J_{5,4}$ 4.8, $J_{5,6}$ 6.4, H-5), 4.40 (1H, p-t, J 4.0 Hz, H-3), 4.58 (1H, d, $J_{2,3}$ 4.0, H-2).

[17] Each sugar residue of a carbopeptoid is labelled alphabetically from the *N*- to the *C*- terminus. Protons on each sugar ring are numbered according to IUPAC recommendations.

[18] 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.

[19] Claridge, T. D. W., Long, D. D., Hungerford, N. L., Smith, M. D., Aplin, R. T., Marquess, D. G., Fleet, G. W. J., *Tetrahedron Lett.*, **1999**, *40*, 2199.

[20] Support from EPSRC, GlaxoWellcome and the European Community [for a post doctoral fellowship (programme training and mobility research - contract no. ERBFMBICT961664)] is gratefully acknowledged.