Pergamon

Tetrahedron Letters 40 (1999) 2195–2198

TETRAHEDRON LETTERS

From Sequencamers to foldamers? Tetrameric Furanose Carbopeptoids from *cis- and trans*-5-Aminomethyl-Tetrahydrofuran-2-carboxylates

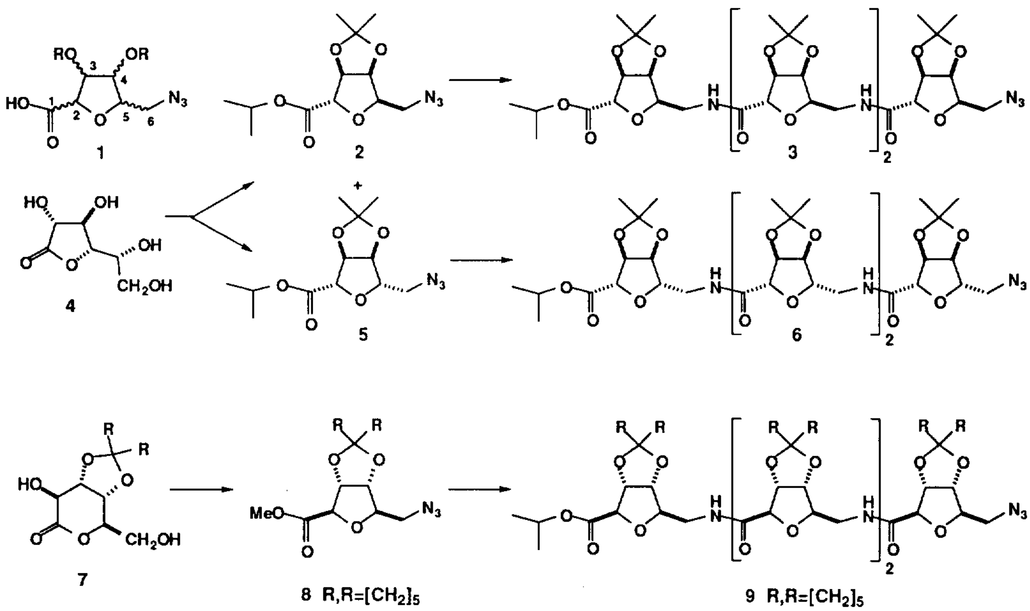
Daniel D. Long,[a] Natasha L. Hungerford,[a] Martin D. Smith,[a] Dominic E. A. Brittain,[a] Daniel G. Marquess,[b,c] Timothy D. W. Claridge[a] and George W. J. Fleet[a*]

[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

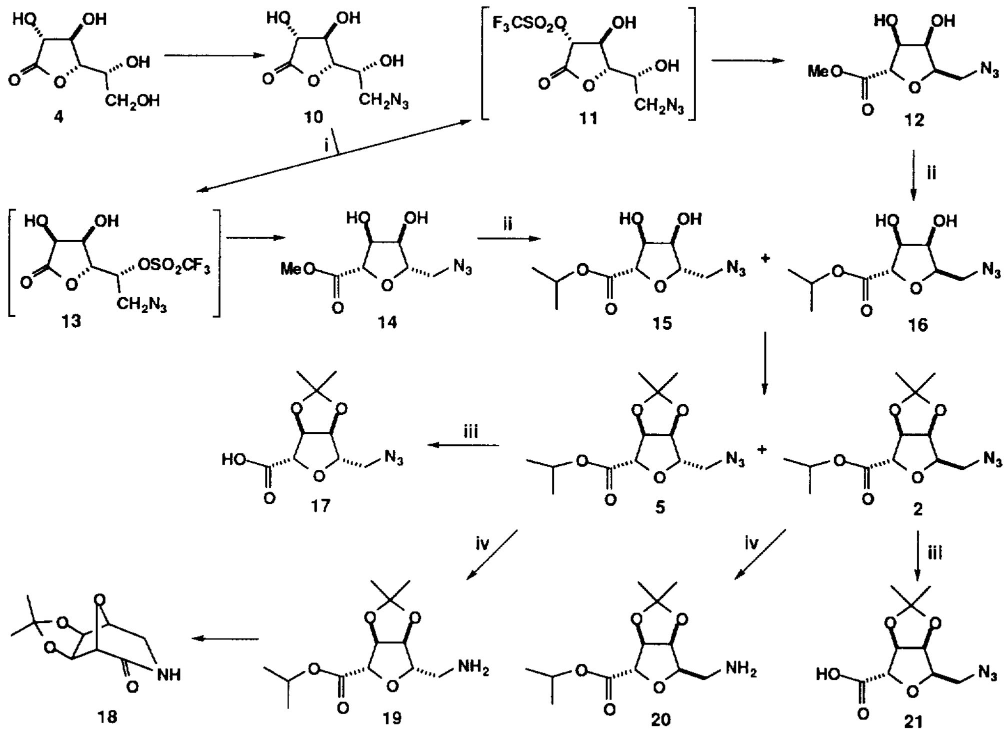
Abstract: The synthesis of three stereoisomeric *cis*- and *trans*-5-azidomethyl-tetrahydrofuran-2-carboxylates in which a ketal-protected *cis*-diol unit is present is described. The monomers undergo efficient oligomerisation to tetrameric carbopeptoids in which the diol protection facilitates ready purification by chromatography which augurs well for the formation of homogeneous higher polymers.

Gellman has suggested the term 'sequencamers' for novel oligomers in which conformational properties are not of central interest and/or have not been investigated; 'foldamers' are polymers which have a tendency to adopt a specific compact conformation.[1] The sixteen stereoisomers of the azidomethyl-tetrahydrofuran carboxylic acid **1** are clearly a family of sequencamer monomers that may provide opportunities for the introduction of novel dipeptide isosteres into combinatorial libraries; evidence is beginning to accrue that they may provide information on constructing guidelines for the design of small ring templates which induce secondary structure in short sequences. Oligomers of one stereoisomer of **1** have been reported to give rise to β-turn-like conformations – even in a trimer – whereas another stereoisomer appears not to induce significant secondary structure in a tetramer.[2] This paper describes the synthesis of a further three stereoisomeric building blocks of **1** together with their conversion to the respective tetramers, all of which give some evidence of secondary structure;[3] they all have a 3,4-*cis*-diol unit which may be efficiently protected as a ketal leading to easy manipulation of the oligomeric materials.



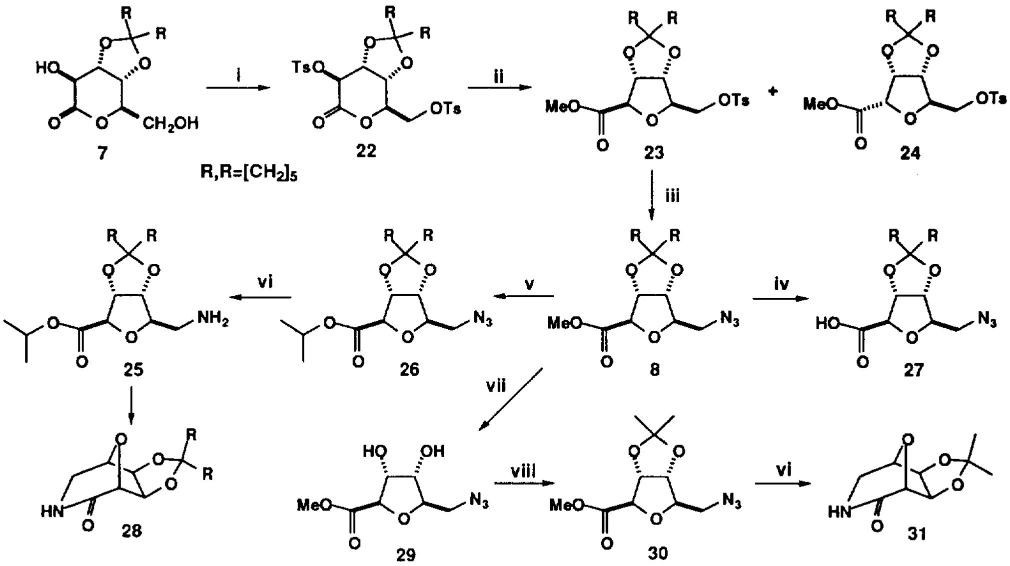
PII: S0040-4039(99)00110-0

D-Galactonolactone **4** was converted into the 6-azidoderivative **10** in an overall yield of 61% as described elsewhere [Scheme 1].[4] Reaction of **10** with triflic anhydride in the presence of pyridine in ethyl acetate, followed by treatment with methanol, gave an inseparable mixture of two epimeric azidomethyl tetrahydrofuran carboxylates **12** and **14** in 46% yield in a ratio of 2.5:1. The product ratio was dependent on the reaction conditions. Formation of the D-*talo*-isomer **12** arises from the expected preferential triflation of **10** at the free C-2 hydroxyl followed by ring opening with methanol and subsequent THF ring formation by displacement of the C-2 triflate with inversion of configuration by the OH group at C-5. The formation of the L-*allo*-isomer **14** was unanticipated as inversion of configuration at both C-2 and C-5 are required in its formation from **10**; a plausible pathway might involve initial epimerisation at C-2 of **10** and triflate ester formation at C-5 to afford the triflate **13** which would then permit formation of the THF ring with the observed stereochemistry from closure by attack of the C-2 OH group onto C-5.



Scheme 1: (i) $(CF_3SO_2)_2O$, pyridine, EtOAc; then add MeOH (ii) HCl, Me_2CHOH; then add Me_2CO (iii) NaOH, H_2O, dioxane; then Amberlite IR-120 (H^+) (iv) H_2, Pd black

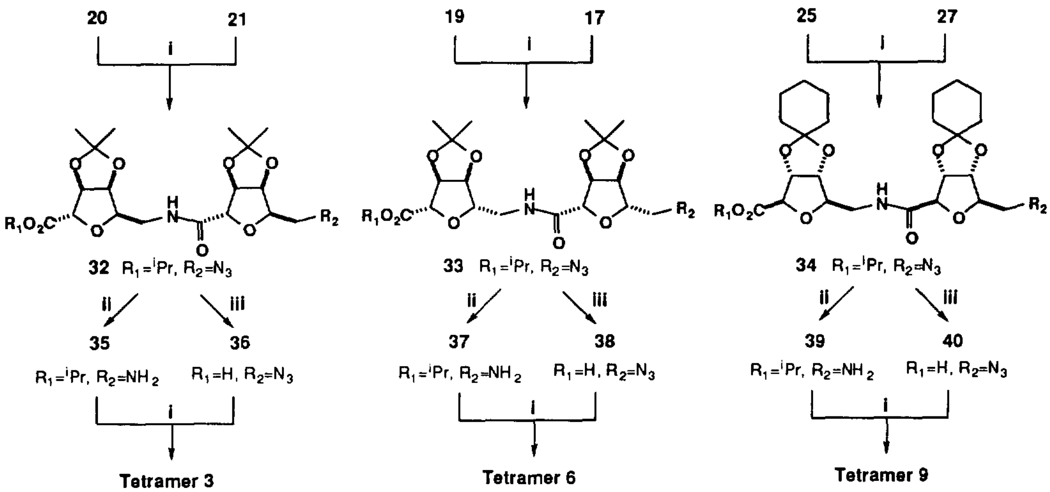
Treatment of the mixture of **12** and **14** with HCl in isopropanol caused efficient transesterification to the isopropyl esters **15** and **16**, still as an inseparable mixture; however, subsequent addition of acetone to the crude reaction mixture of **15** and **16** yielded the separable isopropyl esters as D-*talo*- **2**, $[\alpha]_D^{26}$ −7.0 (*c*, 0.93)[5] [65% yield] and *L-allo*- **5** $[\alpha]_D^{26}$ −23.9 (*c*, 1.04) [23% yield].[6] The major D-*talo*-isomer **2** was converted into the building blocks **21** [by treatment with sodium hydroxide in aqueous dioxane] and **20** [by hydrogenation in the presence of palladium black] required for the formation of oligomers. Analogous treatment of the minor component **5** gave the L-*allo*-acid **17** and amine **19**. The amine **20** with 2,5-*trans*-substituents was relatively stable whereas the 2,5-*cis*-epimer **19** spontaneously cyclised on concentration of the reaction mixture to the tricyclic lactam **18**, m.p. 192°C, $[\alpha]_D^{23}$ −39.2 (*c*, 0.75 in $CHCl_3$), $[\alpha]_D^{22}$ −25.7 (*c*, 0.75 in EtOH); both the ^1H and ^{13}C NMR spectra of **18** were identical to those of its enantiomer **31**. The crude amine **20** in solution could be used directly in the coupling reactions for the formation of oligomers.



Scheme 2: (i) TsCl, pyridine (ii) K_2CO_3, MeOH (iii) NaN_3, DMF (iv) NaOH, H_2O, dioxane; then Amberlite IR-120 (H^+) (v) HCl, Me_2CHOH (vi) H_2, Pd black (vii) H_2O, CF_3COOH (viii) $Me_2C(OMe)_2$, Me_2CO, CSA

For the synthesis of the differently protected enantiomeric tetrahydrofuran **8**, the tetrahydrofuran ring is constructed prior to the introduction of the azide functionality [Scheme 2]. The cyclohexylidene 1,5-lactone **7**, which is more readily available from D-ribose than the corresponding acetonide,[7,8] was esterified with an excess of tosyl chloride in pyridine to afford the ditosylate **22**, m.p. 63-64°C, $[\alpha]_D^{24}$ +13.5 (*c*, 1.35) in 59% yield. Treatment of **22** with potassium carbonate in methanol gave D-*allo*-ester **23**, $[\alpha]_D^{24}$ -11.5 (*c*, 1.13) as the major product in 60% yield, together with a small amount of the D-*altro*-epimer **24**, $[\alpha]_D^{24}$ -7.3 (*c*, 2.55) [19% yield]. The major product **23** arises from ring opening of the lactone followed by ring closure by displacement with inversion of configuration of the tosylate at C-2 by the C-5 OH group; the minor product **24** is formed by an additional base-catalysed epimerisation at C-2, probably prior to formation of the THF ring. Reaction of the tosylate **23** with sodium azide in DMF afforded the fully protected methyl ester **8**, $[\alpha]_D^{24}$ +23.9 (*c*, 1.15) in 89% yield. Hydrolysis of the azidoester **8** with aqueous sodium hydroxide gave the azidoacid **27** as the monomeric acid component for oligomer formation. Hydrogenation of **8** gave the bicyclic lactam **28**, m.p. 213-215°C, $[\alpha]_D^{24}$ +23.3 (*c*, 0.48), so that it was again necessary to change the methyl for the more hindered isopropyl ester; reaction of the methyl ester **8** with a solution of HCl in isopropanol gave the isopropyl ester **26**, $[\alpha]_D^{24}$ +16.0 (*c*, 0.23), in 83% yield. Hydrogenation of the azide **26** in isopropanol in the presence of palladium black gave the corresponding amine **25** which on standing or on concentration of the solvent was converted spontaneously into the tricyclic lactam **28**. However, the crude amine **25** in solution again could be used directly in the coupling reactions for the formation of oligomers.

The cyclohexylidene ester **8** was also converted into the isopropylidene lactam **31** as a structural proof of this series and of its enantiomer **18**. Removal of the cyclohexylidene protecting group in **8** with aqueous trifluoroacetic acid gave **29** which on reaction with dimethoxypropane in acetone in the presence of camphorsulfonic acid (CSA) gave the isopropylidene methyl ester **30**, $[\alpha]_D^{24}$ +28.0 (*c*, 0.45). Subsequent hydrogenation of the azide **30** in methanol in the presence of palladium black afforded the lactam **31**, m.p. 193-195°C, $[\alpha]_D^{24}$ +34.4 (*c*, 0.43), in 68% overall yield with identical ^1H and ^{13}C NMR spectra to those of its enantiomer **18**.



Scheme 3: (i) EDCI, HOBt, DIPEA, CH_2Cl_2 (ii) H_2, Pd black (iii) NaOH, H_2O, dioxane; then Amberlite IR-120 (H^+)

The formation of the tetramers derived from the monomeric building blocks is summarised in Scheme 3. Thus the D-*talo* amine **20** and acid **21** were efficiently coupled with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) in the presence of diisopropylethylamine (DIPEA) in dichloromethane to give the dimer **32**, $[\alpha]_D^{24}$ +3.7 (*c*, 0.77), in 74% yield. Subsequent hydrogenation or hydrolysis of **32** gave the respective amine **35** or acid **36** which underwent iterative coupling to afford the D-*talo*-tetramer **3**, $[\alpha]_D^{24}$ +11.2 (*c*, 0.50), in 79% yield. Similarly, the L-*allo*-amine **19** and acid **17** monomers were coupled to give the dimer **33**, $[\alpha]_D^{23}$ −28.8 (*c*, 0.72), in 58% yield; in this case, the amine **19** is highly susceptible to intramolecular closure to the lactam **18**. Further elaboration of **33** to the L-*allo*-tetramer **6**, $[\alpha]_D^{24}$ -47.4 (*c*, 0.70), proceeded in 75% overall yield. The enantiomeric - but differently protected - amine **25** and acid **27** afforded the dimer **34**, $[\alpha]_D^{24}$ +25.4 (*c*, 1.14), in 73% yield which gave the D-*allo*-tetramer **9**, $[\alpha]_D^{25}$ +43.2 (*c*, 1.59) in 65% yield. All the tetramers are readily purified as homogeneous materials by flash chromatography in ethyl acetate:hexane (1:1), so that such materials are available in a pure form for structural studies.

The following paper presents preliminary evidence that indicates that all the tetramers reported in this paper may be predisposed towards conformations with secondary structures. Additionally, the ease of purifying the tetramers – and the efficiency of the peptide coupling procedures – provide optimism for the availability of purified homogenous higher oligomers and provide the opportunity for the study of secondary structure in well defined highly functionalised families of carbopeptoids.[9]

References.

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

[2] Smith, M. D., Long, D. D., Martin, A., Marquess, D. G., Claridge, T. D. W., Fleet, G. W. J., *Tetrahedron Lett.*, **1999**, *40*, 2191 and references cited therein.

[3] 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.

[4] 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., submitted for publication.

[5] Except where otherwise stated, all compounds in this paper were oils or amorphous solids, and specific rotations were determined in $CHCl_3$ as a solvent.

[6] The yields of **2** and **5** are based on the using the weight of the mixture of methyl esters **12** and **14**.

[7] Bichard, C. J. F., Fairbanks, A. J., Fleet, G. W. J., Ramsden, N. G., Vogt, K., Doherty, O., Pearce, L., Watkin, D. J., *Tetrahedron: Asymm.*, **1991**, *2*, 901.

[8] Fairbanks, A. J., Fleet, G. W. J., *Tetrahedron*, **1995**, *51*, 3881.

[9] Support from EPSRC and GlaxoWellcome is acknowledged.