Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7718–7725
Tetrahedron

A novel series of oligomers from 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-*cis* and 2,4-*trans* stereochemistry

Alison A. Edwards,[a,*] Gangadharar J. Sanjayan,[b] Shuji Hachisu,[c] George E. Tranter[a] and George W. J. Fleet[c]

[a]*Biological Chemistry, Division of Biomedical Sciences, Imperial College, London SW7 2AZ, UK*
[b]*Division of Organic Synthesis, National Chemical Laboratory, Pune 411 008, India*
[c]*Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*

Received 22 March 2006; revised 9 May 2006; accepted 25 May 2006
Available online 16 June 2006

Abstract—Two tetrahydrofuran-based γ-amino acids [2,4-*cis* and 2,4-*trans*] were subjected to iterative peptide-coupling procedures to afford dimeric, tetrameric and hexameric carbopeptoids in good yield. These homooligomers were prepared for secondary structural study—to ascertain the conformational preference inherent in the monomer units. The L-*xylo* oligomers were protected with triethylsilyl ethers to increase the range of solvents suitable for structural investigation. Initial secondary structure data indicate the presence of hydrogen-bonded conformations in the L-*ribo* series.

1. Introduction

Peptides and proteins are coded by sequences of α-amino acids but efforts to decipher this complexity has only been partially successful.[1] Peptides are key to the development of new drugs however the low oral bioavailability of peptides has been a long-standing issue.[2,3] Initial synthetic efforts to circumvent this issue focused on the chemical modification of peptide libraries; more recent synthetic endeavours have led to an ever-expanding catalogue of peptidomimetics. Numerous β-amino acids, homologues of α-amino acids have been prepared and their oligomers extensively studied. These have been found to be stable to proteolytic enzymes and adopt an array of secondary structures akin to those observed in α-peptides (see Fig. 1a).[4–10] This concept has been expanded to include γ- and δ-amino acids; δ-amino acids may be regarded as dipeptide isosteres.[11,12] γ-Amino acids are found in nature, e.g., γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter and tubulysins are potent antimitotic agents.[13,14]

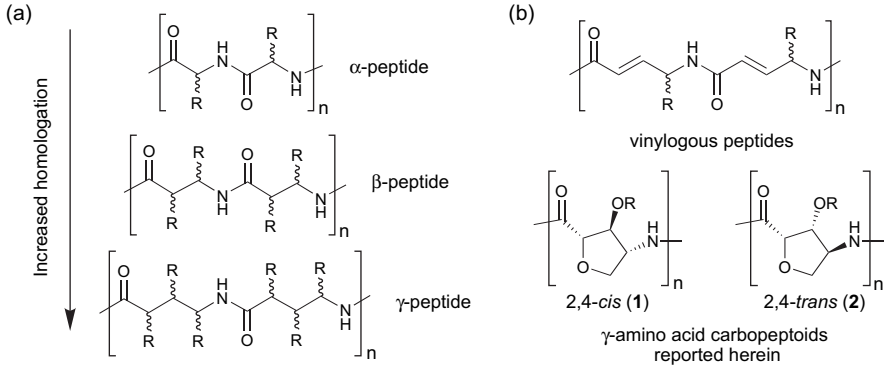


Figure 1. (a) From α-peptides to γ-peptides and (b) examples of γ-peptides.

Keywords: Sugar amino acids; Peptidomimetics; Gamma amino acids; Foldamers.
* Corresponding author. Tel.: +44 20 7594 3143; fax: +44 20 7594 3226; e-mail: alison.edwards@imperial.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.067

Acyclic γ-amino acids of vinylogous systems and their corresponding saturated analogues, have been prepared employing various side chains and substitution patterns to achieve structural diversity.[15–18,10,11] In addition to the adoption of an array of peptide-like secondary structures and resistance to proteolytic degradation,[19–21,9,10] a γ-dipeptide was found to exhibit affinity for human somatostatin receptors.[22] Oligomers of ureas, carbamates, phosphodiesters and vinylogous sulfonamidopeptides have also been prepared as γ-peptide analogues.[23] The first cyclically constrained γ-amino acids were prepared as GABA analogues and based upon a cyclopentane scaffold; the enantiomer was employed by Woll et al. to prepare a parallel sheet secondary structure.[24,25] Furanose-based and sugar-fused GABA analogues have since been prepared.[24,26] More recent synthetic efforts have included cyclic scaffolds, which are (poly)hydroxylated cyclohexanes,[27,28] contain a lactam[29] or are based on proline, cyclopropane or bicylic scaffolds.[30–32]

Sugar scaffolds with amine and carboxylic acid moieties, aka sugar amino acids (SAAs), have been used to create cyclically constrained α-, β-, γ-, δ- and ε-amino acids.[33–36] SAAs have been employed as peptidomimetics[37–39] and library scaffolds and their oligomers (carbopeptoids) examined as foldamers, which can adopt an array of secondary structures such as helices and β-turns.[40–43] Kessler et al. have reported a pyranose-based γ-SAA, which predetermines a β-turn conformation in synthetic peptides[36] and a heterooligomer composed of a furanose γ-SAA and GABA, with no stable conformation in solution.[44] Furanose- and pyranose-based γ-SAAs have been utilised to prepare 99-member and 384-member libraries, respectively.[45,46]

Recently, our group has reported the synthesis of two new furanose γ-SAA scaffolds,[47–49] herein we report the preparation of the oligomers of β-hydroxy γ-azido esters (see Fig. 1b). The dimer arising from the 2,4-*cis*-SAA (**3**) was shown to adopt a γ-turn type conformation in solid phase. γ-Turns in α-peptides require three residues and are stabilised by a hydrogen bond from CO^{i} to NH^{i+2};[50,51] they exist as two possible enantiomers with respect to the main chain structure, the inverse turn being more common than the classic turn. Studies of existing protein data[52] and prediction attempts[53,54] have been conducted in an attempt to understand the features that govern such turns. Mimics of γ-turns have been prepared[55–60] and analogues of bradykinin,[61] the peptide hormone vasopressin[62] and angiotensin receptor ligands[63] based on γ-turn mimics. Several different strategies have been reported in the attempt to prepare γ-turns.[64,65]

2. Results and discussion

2.1. Strategy

γ-Azido esters **1** and **2** have been prepared as part of the ongoing search for peptidomimetics with secondary structural preferences.[49,47] To investigate the conformational preferences of the γ-azido esters, they require to be coupled to form homooligomers. These homooligomers can be studied using solution- and solid-phase techniques to ascertain whether the oligomers adopt compact secondary structures in relatively short sequences, i.e., are foldamers.[40]

The L-*ribo* γ-azido ester **1** and L-*xylo* γ-azido ester **2** are available in seven steps starting from the acetonide of L-arabinose **5** and D-ribose **6**, respectively (Fig. 2).[47,49] The homooligomers of THF γ-azido esters **1** and **2** were prepared using established solution-phase coupling procedures with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) as the coupling agent.[66] The formation of the tetrameric and hexameric homooligomers was achieved via an iterative approach.

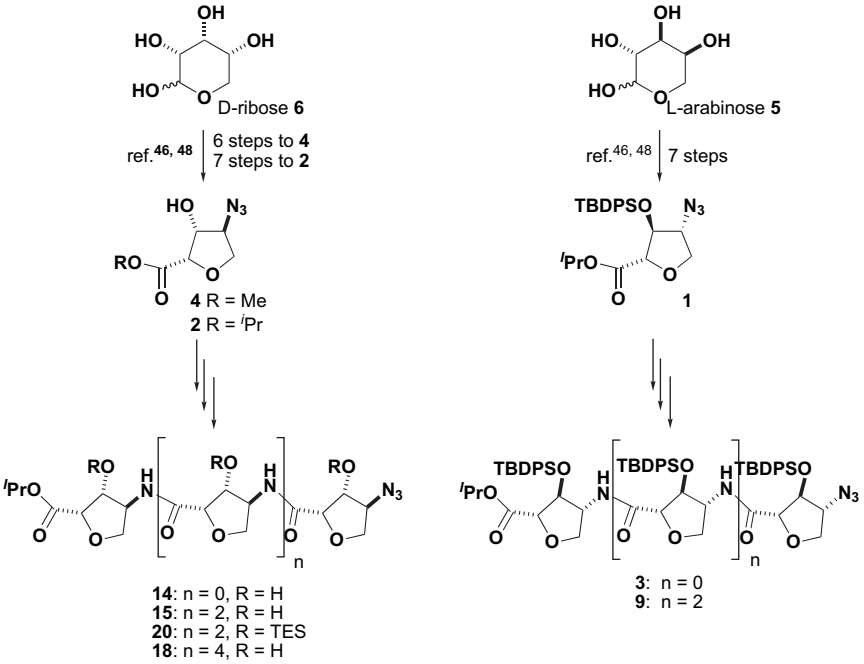


Figure 2. Homooligomers from the 2,4-*cis* and 2,4-*trans* γ-azido esters (**1** and **2**, respectively).

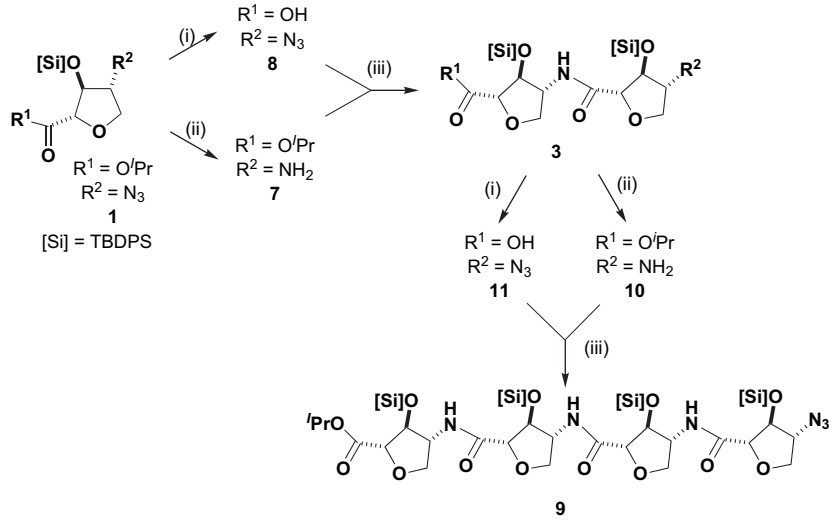
2.2. Synthesis of homooligomers from the L-*ribo* γ-azido ester 1

Hydrogenation of the azido group in isopropyl L-*ribo* γ-azide **1** with 10% palladium on carbon in propan-2-ol proceeded smoothly to afford amine **7**, which was used without further purification (Scheme 1). Hydrolysis of the ester functionality in **1** with aqueous methanolic potassium hydroxide followed by short exposure to Amberlite H^+ resin generated the desired acid **8**. Acid **8** was coupled to amine **7** using standard peptide-coupling conditions with TBTU and *N*,*N*-diisopropylethylamine (DIPEA) in *N*,*N*-dimethylformamide (DMF) to yield dimer **3** in 80% yield from azide **1**. The structure of dimer **3** was confirmed by X-ray crystallography.[67]

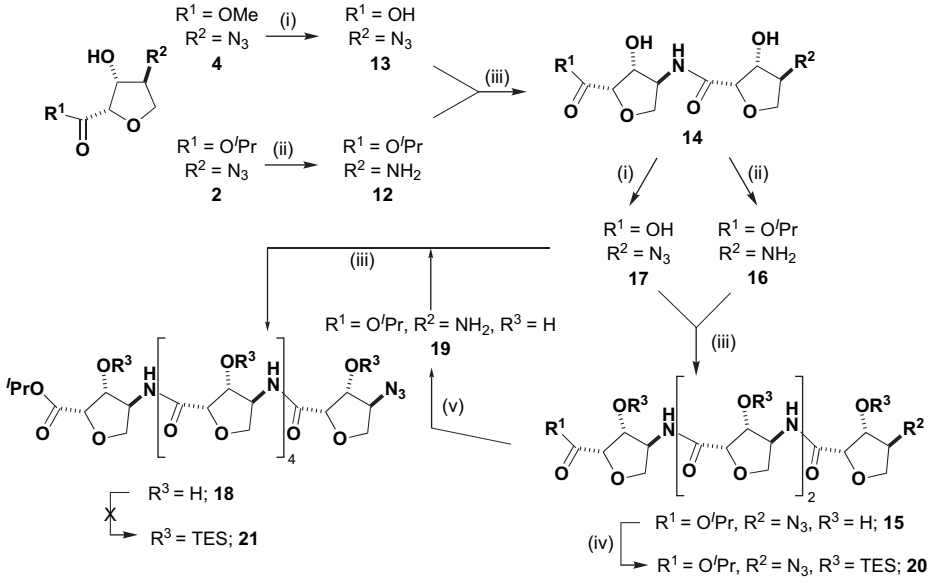
An iterative approach was adopted to synthesise the tetrameric carbopeptoid **9**; thus the azide function of dimer **3** was reduced by hydrogenation in propan-2-ol in the presence of 10% palladium on carbon to afford the N-terminal amine **10**. Treatment of dimer **3** with aqueous methanolic potassium hydroxide followed by short exposure to Amberlite H^+ resin gave access to acid **11**, which was coupled to amine **10** with TBTU/DIPEA in DMF. Purification of the crude product by flash chromatography afforded tetramer **9**, albeit in poor yield (26%).

2.3. Synthesis of homooligomers from the L-*xylo* γ-azido ester 2

Amine **12** was afforded by hydrogenation of the azido group in the isopropyl L-*xylo* γ-azide **2** with 10% palladium on carbon in propan-2-ol and was used without further purification (Scheme 2). Hydrolysis of the ester functionality in the methyl L-*xylo* γ-azide **4** was achieved with aqueous sodium hydroxide in dioxane with subsequent treatment with Amberlite H^+ resin to give the desired acid **13**. Acid **13** was coupled to amine **12** with TBTU and triethylamine



Scheme 1. *Reagents and conditions*: (i) KOH, MeOH, H_2O, rt then Amberlite IR-120 (H^+) resin; (ii) 10% Pd/C, propan-2-ol, H_2, rt; (iii) DIPEA, TBTU, DMF, rt.



Scheme 2. *Reagents and conditions*: (i) NaOH, dioxane, H_2O, rt then Amberlite IR-120 (H^+) resin; (ii) 10% Pd/C, propan-2-ol, H_2, rt; (iii) TEA, TBTU, DMF, rt; (iv) TES-OTf, pyridine, −20 °C to rt, 14 h; (v) 10% Pd/C, DMF, H_2, rt.

(TEA) in DMF to yield the desired dimer **14** in 61% yield from the azide (**2** or **4**).

Tetramer **15** was prepared from the amine and acid derived from dimer **14**. The azide function of dimer **14** was reduced by hydrogenation in propan-2-ol in the presence of 10% palladium on carbon to afford the N-terminal amine **16**. Treatment of dimer **14** with aqueous sodium hydroxide in dioxane followed by short exposure to Amberlite H^+ resin gave access to acid **17**, which was coupled to amine **16** using TBTU/TEA in DMF. Purification of the crude product by flash chromatography and size exclusion chromatography afforded tetramer **15** in good yield (60%).

Hexamer **18** was prepared from the amine derived from tetramer **15** and acid **17** derived from dimer **14**. The azide function of tetramer **15** was reduced by hydrogenation in DMF (**15** was not soluble in propan-2-ol) in the presence of 10% palladium on carbon to afford the N-terminal amine **19**. Acid **17** was coupled to amine **19** with TBTU/TEA in DMF. Purification of the crude product by flash chromatography and size exclusion chromatography afforded hexamer **18,** albeit in poor yield (25%).

2.4. Protection of the free hydroxyls of the homooligomers (from 2)

Protection of the free hydroxyls of tetramer **15** and hexamer **18** would enable further investigation of the secondary structural preference of the systems. The hydroxyl derivatisation would enable solubilisation of the homooligomers in solvents such as chloroform and would enable solution-state IR spectra to be recorded. Triethylsilyl ethers were chosen for hydroxyl protection as they are related to the protection used in the L-*ribo* homooligomers. More importantly, they do not contain the phenyl residues, which complicate observation of amide protons by ^{1}H NMR spectroscopy and study of the amide chromophores by circular dichroism.

The silyl protection of tetramer **15** was achieved by treatment of **15** with a large excess of triethylsilyl trifluoromethanesulfonate in pyridine (Scheme 2). Purification via flash chromatography on basic alumina afforded the silylated tetramer **20** in 13% yield. Attempts to protect hexamer **18** in a similar manner were unsuccessful—no silylated products were observed by electrospray mass spectrometry. The poor yields achieved for the silylation of the homooligomers may be related to steric hindrance due to the bulkiness of the triethylsilyl group. Sufficient material was isolated from the silylated tetramer **20** to allow secondary structure investigation.

2.5. Secondary structure

Initial examination of ^{1}H NMR spectroscopic and crystallographic data provided important secondary structural evidence. The X-ray crystal structure of dimer **3** revealed a hydrogen-bonded turn conformation akin to that of a γ-turn (see Fig. 3).[67] The high δ_{NH} of **3** by ^{1}H NMR spectroscopy ($CDCl_3$, 500 MHz) indicated that this conformation may also be present in solution. Further to this, the corresponding tetramer **9** has similar high δ_{NH} (benzene-d_6, 500 MHz) for NH^B and NH^C suggesting that it may adopt a related

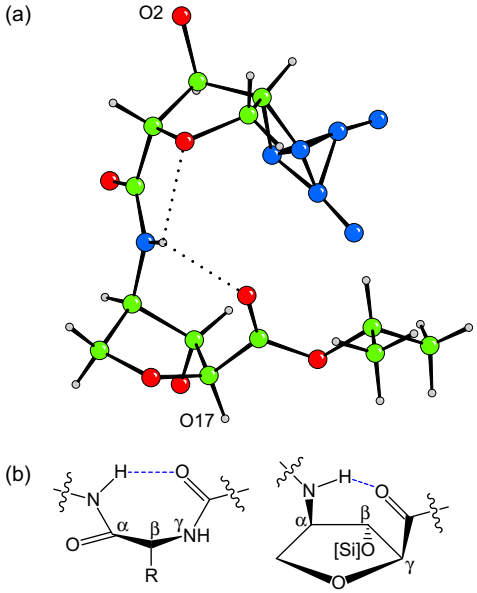


Figure 3. (a) The solid-state conformation of dimer **3**, as revealed by single crystal X-ray diffraction, clearly showing a seven-membered ring hydrogen-bonded γ-turn like structure. The hydrogen bonds are shown as dotted lines. TBDPS groups attached to O2 and O17 have been omitted for clarity. Note that the azide group (N_3) is not fully refined; (b) γ-Turns in an α-peptide and SAA dimer **3**.

hydrogen-bonded conformation. In contrast to the L-*ribo* series, the L-*xylo* oligomers have relatively low δ_{NH} suggesting the absence of a hydrogen-bonded conformation. A full secondary structural study of these oligomers will be reported in due course.

3. Conclusion

Tetrahydrofuran-based γ-amino acids (2,4-*cis* **1** and 2,4-*trans* **2**) were subjected to iterative peptide-coupling procedures to afford dimeric, tetrameric and hexameric carbopeptoids in good yield. These homooligomers were prepared to enable secondary structural study—to ascertain the conformational preference inherent in the monomer units **1** and **2**. Such information is of great significance for the design of compounds with predisposed conformation, e.g., peptidomimetics and nanomaterials.

4. Experimental

4.1. General

The general methods used have been described previously[49] although there are several further comments. Reactions were performed under an atmosphere of nitrogen or argon, unless stated otherwise. Sheets were visualised using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 0.5% ninhydrin in methanol (particularly for amines). Flash chromatography was performed on Sorbsil C60 40/60 silica and, where stated, on basic alumina [Actal UGI (aluminium oxide—activated) from Rockwood Additives Ltd.]. Size exclusion chromatography was performed using Sephadex LH-20. For NMR assignment of the furanose residues, the residues were labelled sequentially from the N to C terminus, e.g., in a tetramer, residue A

contains the azide and residue D contains the ester. Residual signals from the solvents were used as an internal reference. ^{1}H and ^{13}C spectral assignments were achieved using a combination of COSY, TOCSY, HSQC, Tr-ROESY and HMBC. ^{13}C data have been quoted to two decimal places for several oligomers to clarify the assignment given.

4.1.1. Isopropyl 4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonyl)-4-deoxy-L-ribonate 3. A solution of isopropyl 2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonate **1** (0.39 g, 0.86 mmol) in propan-2-ol (10 mL) containing palladium (10 wt % on carbon, 50 mg) was vigorously stirred under an atmosphere of hydrogen. After 13 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.42) and the presence of a major product (R_f 0.12). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford amine **7** as a colourless oil, which was used without further purification.

Potassium hydroxide (0.063 g, 1.1 mmol) was added to a stirred solution of isopropyl azido ester **1** (0.39 g, 0.86 mmol) in methanol (5 mL) containing water (1 mL). After 16 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.42). The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 2 min and filtered. The filtrate was concentrated in vacuo to afford acid **8** as a colourless oil, which was used without further purification.

DIPEA (0.31 mL, 1.8 mmol) and TBTU (0.57 g, 1.71 mmol) were added to a stirred solution of acid **8** and amine **7** in DMF (2 mL). After 23 h, TLC (dichloromethane) revealed the formation of a major product (R_f 0.42). The mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:9) to yield dimer **3** as a white solid (0.58 g, 80%): mp 127–128 °C (MeOH); $[\alpha]_D^{23}$ +91.0 (*c* 0.51 in $CHCl_3$); (HRMS (ESI+ve): Found 843.3572. $C_{45}H_{56}N_4O_7Si_2Na$ ($M+Na^+$) requires *m/z*, 843.3580); Isotope distribution *m/z* (ES+ve) found: 843.36 (100), 844.29 (60), 845.31 (20%). $C_{45}H_{56}N_4O_7Si_2Na$ ($M+Na^+$) requires: 843 (100), 844 (61), 845 (26%); ν_{max} (thin film): 3360 (NH, amide), 2106 (N_3), 1738 (C=O, ester), 1681 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 0.97 (3H, d, *J* 6.3, $CH(CH_3)_2$), 1.10 (9H, s, $SiC(CH_3)_3$), 1.15 (9H, s, $SiC(CH_3)_3$), 1.16 (3H, d, *J* 6.3, $CH(CH_3)_2$), 3.51 (1H, d, *J* 3.9, H-4^A), 3.89 (1H, d, $J_{5A,5'A}$ 9.7, H-5^A), 4.04 (1H, d, *J* 9.0, H-5^B), 4.15 (1H, dd, $J_{5'A,4A}$ 3.9, $J_{5A,5'A}$ 9.7, H-$5'^A$), 4.18 (1H, br s, H-3^B), 4.32 (1H, br s, H-2^B), 4.36 (1H, dd, *J* 4.4, *J* 9.1, H-$5'^B$), 4.45 (1H, br s, H-2^A), 4.56 (1H, br s, H-3^A), 4.60 (1H, a-dd, *J* 4.2, *J* 10.0, H-4^B), 4.87 (1H, sept, *J* 6.3, $CH(CH_3)_2$), 7.26–7.41 (6H, m, 6×Ar*H*), 7.42–7.48 (7H, m, NH^B and 6×Ar*H*), 7.60–7.80 (8H, m, 8×Ar*H*); δ_C ($CDCl_3$, 125.7 MHz) 19.0 ($SiC(CH_3)_3$), 19.1 ($SiC(CH_3)_3$), 21.3 ($CH(CH_3)$), 21.7 ($CH(CH_3)$), 26.7 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 56.7 (C-4^B), 66.7 (C-4^A), 69.1 ($CH(CH_3)_2$), 71.7 (C-5^A), 73.8 (C-5^B), 80.4 (C-3^A), 81.3 (C-3^B), 84.8 (C-2^B), 85.2 (C-2^A), 127.6, 127.7, 127.8, 128.0 (8×Ar*C*H), 129.8, 129.9, 130.2, 130.2 (4×Ar*C*H), 132.1, 132.2, 132.9, 133.1 (4×Ar*C*), 135.6, 135.7, 135.9 (8×Ar*C*H), 168.4 (C=O^A), 171.1 (C=O^B); *m/z* (ESI+ve): 879 (100%, $M+MeCN+NH_4^+$).

4.1.2. Isopropyl 4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonyl)-4-deoxy-L-ribonyl)-4-deoxy-L-ribonyl)-4-deoxy-L-ribonate 9. A solution of dimer **3** (0.16 g, 0.19 mmol) in propan-2-ol (10 mL) containing palladium (10 wt % on carbon, 50 mg) was vigorously stirred under an atmosphere of hydrogen. After 15 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.40) and the presence of a major product (R_f 0.10). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford dimer-amine **10** as colourless oil, which was used without further purification.

Potassium hydroxide (0.014 g, 0.25 mmol) was added to a stirred solution of dimer **3** (0.16 g, 0.19 mmol) in methanol (5 mL) containing water (1 mL). After 20 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.40). The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 2 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **11** as colourless oil, which was used without further purification.

DIPEA (0.043 mL, 0.25 mmol) and TBTU (0.08 g, 0.25 mmol) were added to dimer-amine **10** and dimer-acid **11** in dry DMF (1 mL). After 28 h, TLC (ethyl acetate–pet. ether, 3:1) revealed the formation of a major product (R_f 0.56). The mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:9) to yield tetramer **9** as a white solid (0.056 g, 26%); mp 74–75 °C (MeOH); $[\alpha]_D^{23}$ +70.8 (*c* 0.5 in $CHCl_3$); Isotope distribution *m/z* (ES+ve) found: 1555.74 (70), 1556.63 (90) 1557.68 (70), 1558.58 (35), 1559.19 (20%). $C_{87}H_{106}N_6O_{13}Si_4Na$ ($M+Na^+$) requires: 1555 (76), 1556 (90) 1557 (65), 1558 (32), 1559 (15%); ν_{max} (thin film): 3386 (NH, amide), 2106 (N_3), 1727 (C=O, ester), 1668, 1679, 1692 (C=O, amide) cm^{-1}; δ_H (C_6D_6, 500 MHz) 0.73 (3H, d, *J* 6.2, $CH(CH_3)_2$), 0.82 (3H, d, *J* 6.2, $CH(CH_3)_2$), 1.13 (9H, s, $SiC(CH_3)_3$), 1.15 (9H, s, $SiC(CH_3)_3$), 1.18 (9H, s, $SiC(CH_3)_3$), 1.19 (9H, s, $SiC(CH_3)_3$), 3.14 (1H, d, *J* 3.8, H-4^A), 3.56 (1H, d, *J* 9.8, H-5^A), 3.64 (1H, d, *J* 9.2, H-5^D), 3.68 (1H, dd, *J* 3.7, 6.1, H-$5'^A$), 3.70 (1H, br s, H-5^C), 3.81 (1H, d, *J* 8.9, H-5^B), 4.10–4.14 (2H, m, H-$5'^B$ and H-$5'^C$), 4.17 (1H, dd, *J* 4.2, 9.2, H-$5'^D$), 4.25 (1H, d, *J* 1.15, H-2^C), 4.35 (1H, q, *J* 4.1, H-4^D), 4.40 (1H, br s, H-2^B), 4.42 (1H, br s, H-2^D), 4.51 (1H, br s, H-3^C), 4.55 (1H, br s, H-3^D), 4.59–4.64 (2H, m, H-4^B and H-3^C), 4.65 (1H, br s, H-2^A), 4.72 (1H, sept, *J* 6.2, $CH(CH_3)_2$), 4.78 (1H, m, H-4^B), 4.80 (1H, br s, H-3^A), 6.50 (1H, d, *J* 8.3, NH^D), 7.20–7.36 (24H, m, 24×Ar*H*), 7.49 (1H, d, *J* 9.1, NH^C), 7.69 (2H, m, 2×Ar*H*), 7.73 (2H, m, 2×Ar*H*), 7.78–7.85 (13H, m, NH^B and 12×Ar*H*); δ_C (C_6D_6, 125.7 MHz) 19.62, 19.62, 19.69, 19.73 (4×$SiC(CH_3)_3$), 21.70 ($CH(CH_3)_2$), 27.34, 27.39, 27.48, 27.52 (4×$SiC(CH_3)_3$), 57.93, 58.13, 58.2 (C-4^B, C-4^C and C-4^D), 67.22 (C-4^A), 69.49 ($CH(CH_3)_2$), 71.99 (C-5^A), 73.39 (C-5^D), 73.99 (C-5^C), 74.26 (C-5^B), 81.57 (C-3^A and C-3^D), 81.87 (C-3^C), 82.50 (C-3^B), 85.31 (C-2^D), 86.70 (C-2^A), 87.10, 87.32 (C-2^B and C-2^C), 128.52, 128.56, 128.61, 128.68, 128.70, 128.76, 128.80 (16×Ar*C*H), 130.49, 130.53, 130.69, 130.75, 130.85,

130.89 (8×Ar*C*H), 133.06, 133.29, 133.41, 133.44 133.84, 133.88, 134.06, 134.18 (8×Ar*C*), 136.43, 136.50, 136.53, 136.60, 136.65, 136.68, 136.71 (16×Ar*C*H), 169.01 (C=O^{B}), 170.05 (C=O^{C}), 170.12 (C=O^{D}), 171.91 (C=O^{A}).

4.1.3. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 14. A solution of isopropyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate **2** (221 mg, 1.03 mmol) in propan-2-ol (11 mL) containing palladium (10 wt % on carbon, 23 mg) was vigorously stirred under an atmosphere of hydrogen. After 5 h, TLC (ethyl acetate–pet. ether, 2:1) showed the absence of the starting material (R_f 0.5) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford amine **12** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 1.2 mL) was added to a stirred solution of methyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate **4** (192 mg, 1.03 mmol) in dioxane (1.2 mL) and water (2.4 mL). After 3 h, TLC (ethyl acetate–pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford acid **13** as a colourless oil, which was used without further purification.

Triethylamine (204 μL, 1.45 mmol) and TBTU (406 mg, 1.26 mmol) were added to a stirred solution of amine **12** and acid **13** in DMF (11 mL). After 12 h, TLC (ethyl acetate) revealed the formation of a major product (R_f 0.2) and a minor product (R_f 0.3). The reaction mixture was concentrated in vacuo and redissolved in water (30 mL). Chloroform was added to the solution and the organic layer was extracted with water. The combined aqueous extracts were concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:1) to yield dimer **14** (216 mg, 61%) as a white solid: mp 48–49 °C; $[\alpha]_D^{24}$ −25.9 (*c* 1.03 in $CHCl_3$); (HRMS (CI+ve): Found 345.1410. $C_{13}H_{21}N_4O_7$ (M+H$^+$) requires *m/z*, 345.1410); ν_{max} (thin film): 3392 (OH), 2108 (N_3), 1739 (C=O) 1652, 1538 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 1.26 (3H, d, *J* 6.2, CH(CH_3)$_2$), 1.27 (3H, d, *J* 6.2, CH(CH_3)$_2$), 3.84 (1H, dd, $J_{4B,5B}$ 1.7, $J_{5B,5'B}$ 9.8, H-5^B), 3.94 (1H, d, $J_{5A,5'A}$ 9.8, H-5^A), 4.13 (1H, d, $J_{4A,5'A}$ 4.5, H-4^A), 4.24–4.27 (2H, m, H-5′^{A} and H-4^B) 4.37 (1H, dd, $J_{4B,5'B}$ 4.8, $J_{5B,5'B}$ 9.8, H-5′^{B}), 4.48 (2H, m, H-2 and O*H*), 4.53–4.57 (3H, m, H-2, H-3^A and H-3^B), 4.64 (1H, d, *J* 2.5, O*H*), 5.11 (1H, sept, *J* 6.2, C*H*(CH$_3$)$_2$), 7.03 (1H, d, *J* 6.4, NH^B); δ_C ($CDCl_3$, 125.7 MHz) 22.0, 22.1 (CH(*C*H$_3$)$_2$), 58.3 (C-4^B), 66.9 (C-4^A), 69.4 (*C*H(CH$_3$)$_2$), 71.4 (C-5^B), 71.8 (C-5^A), 75.9, 77.0 (C-3^A and C-3^B), 80.6, 82.3 (C-2^A and C-2^B), 169.4 (C=O^B), 170.9 (C=O^A); *m/z* (APCI+ve) 303 (100), 345 (M+H$^+$, 64%).

4.1.4. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 15. A solution of dimer **14** (100 mg, 0.29 mmol) in propan-2-ol (3 mL) containing palladium (10 wt % on carbon, 21 mg) was vigorously stirred under an atmosphere of hydrogen. After 23 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford dimer-amine **16** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 344 μL) was added to dimer **14** (100 mg, 0.29 mmol) in dioxane (0.4 mL) and water (0.7 mL). After 3 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **17** as a colourless oil, which was used without further purification.

Triethylamine (56 μL, 0.40 mmol) and TBTU (112 mg, 0.35 mmol) were added to a stirred solution of dimer-amine **16** and dimer-acid **17** in DMF (3 mL). After 19 h, TLC (ethyl acetate–methanol, 7:3) revealed the formation of a major product (R_f 0.5). The reaction mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–methanol–water, 4:6:3). The resulting residue was further purified by size exclusion chromatography (methanol), to yield tetramer **15** (105 mg, 60%) as a white solid: mp 170–171 °C (decomp.); $[\alpha]_D^{24}$ −13.4 (*c* 1.06 in MeOH); (HRMS (CI+ve): Found 603.2262. $C_{23}H_{35}N_6O_{13}$ (M+H$^+$) requires *m/z*, 603.2262); Isotope distribution *m/z* (ES+ve) found: 625.28 (100), 626.23 (28), 627.25 (7%). $C_{23}H_{34}N_6O_{13}Na$ (M+Na$^+$) requires: 625.20 (100), 626.21 (25), 627.21 (2%); ν_{max} (KBr): 3400 (OH), 2111 (N_3), 1736 (C=O), 1655, 1541 (C=O, amide) cm^{-1}; δ_H (C_5D_5N, 500 MHz) 1.17 (3H, d, *J* 6.3, CH(CH_3)$_2$), 1.20 (3H, d, *J* 6.3, CH(CH_3)$_2$), 3.93 (1H, d, $J_{5A,5'A}$ 9.2, H-5^A), 4.03–4.05 (2H, m, H-5^B and H-5^D), 4.12 (1H, dd, $J_{4C,5C}$ 2.2, $J_{5C,5'C}$ 9.0, H-5^C), 4.31–4.36 (2H, m, H-4^A and H-5′^{A}), 4.39–4.42 (2H, m, H-5′^{B} and H-5′^{D}), 4.60 (1H, dd, $J_{4C,5'C}$ 5.3, $J_{5C,5'C}$ 9.0, H-5′^{C}), 4.85–4.91 (5H, m, H-2^A H-3^A, H-4^B, H-4^C and H-4^D), 4.97–5.00 (3H, m, H-2^B, H-2^D and H-3^C), 5.11 (1H, m, H-2^C), 5.13–5.15 (2H, m, H-3^B and H-3^D), 5.20 (1H, sept, *J* 6.3, C*H*(CH$_3$)$_2$), 8.45 (1H, d, *J* 7.2, NH^C), 8.47 (1H, d, *J* 7.1, NH^B), 8.53 (1H, d, *J* 6.7, NH^D); δ_C (C_5D_5N, 125.7 MHz) 22.2, 22.3 (CH(*C*H$_3$)$_2$), 59.2, 59.2, 59.3 (C-4^B, C-4^C and C-4^D), 68.3 (C-4^A), 68.5 (*C*H(CH$_3$)$_2$), 71.9 (C-5^A), 72.3 (C-5^C), 72.4, 72.5 (C-5^B and C-5^D), 76.4 (C-3), 77.2 (C-3^A), 77.3 (C-3), 77.8 (C-2^C), 82.0 (C-3^C), 83.5, 83.5, 83.5 (C-2^B, C-2^A and C-2^D), 170.4 (C=O^C), 170.5 (C=O^D), 170.9 (C=O^A), 171.0 (C=O^B).

4.1.5. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 18. A solution of tetramer **15** (43 mg, 0.07 mmol) in DMF (5 mL) containing palladium (10 wt % on carbon, 8 mg) was vigorously stirred under an atmosphere of hydrogen. After 3 h, TLC (ethyl acetate–methanol, 7:3) showed the

absence of the starting material (R_f 0.5) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: DMF). The filtrate was concentrated in vacuo to afford tetramer-amine **19** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 85 μL) was added to a stirred solution of dimer **14** (100 mg, 0.29 mmol) in dioxane (85 μL) and water (171 μL). After 3 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **17** as colourless oil, which was used without further purification.

Triethylamine (14 μL, 0.10 mmol) and TBTU (28 mg, 0.09 mmol) were added to a stirred solution of tetramer-amine **19** and dimer-acid **17** in DMF (0.5 mL). After 13 h, TLC (acetonitrile–water, 9:1) revealed the formation of a major product (R_f 0.2). The reaction mixture was concentrated in vacuo and purified by flash chromatography (acetonitrile–water, 9:1). The resulting residue was further purified by size exclusion chromatography (methanol) to yield hexamer **18** (15 mg, 25%) as a white solid: mp 159–160 °C; $[\alpha]_D^{24}$ −33.8 (*c* 0.24 in MeOH); (HRMS (CI+ve): Found 883.2933. $C_{33}H_{48}N_8O_{19}Na$ ($M+Na^+$) requires *m/z*, 883.2933); Isotope distribution *m/z* (ES+ve) found: 883.36 (100), 884.28 (39), 885.28 (8%). $C_{23}H_{34}N_6O_{13}Na$ ($M+Na^+$) requires: 883 (100), 884 (40), 885 (12%); ν_{max} (KBr): 3394 (OH), 2111 (N_3), 1737 (C═O), 1661, 1534 (C═O, amide) cm^{-1}; δ_H (C_5D_5N, 500 MHz) 1.18 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.21 (3H, d, *J* 6.5, $CH(CH_3)_2$), 3.94 (1H, d, $J_{5,5'}$ 9.2, H-5), 4.02–4.06 (3H, m, 4×H-5), 4.13 (1H, dd, $J_{4,5'}$ 2.1, *J* 8.8, H-5), 4.32–4.43 (6H, m, H-4^A and 5×H-5′), 4.62 (1H, dd, $J_{4,5'}$ 5.1, $J_{5,5'}$ 8.8, H-5′), 4.87–5.10 (17H, m, 6×H-2, 6×H-3 and 5×H-4), 5.22 (1H, sept, *J* 6.5, $CH(CH_3)_2$), 8.35–8.38 (4H, m, 4×NH), 8.51 (1H, d, *J* 6.4, NH); δ_C (C_5D_5N, 125.7 MHz) 22.26, 22.31 ($CH(CH_3)_2$), 59.19, 59.26, 59.32 (6×C-4), 68.35, 68.39, 71.92, 72.33, 72.54, 72.58, 72.62 (6×C-5 and $CH(CH_3)_2$), 76.43, 77.30, 77.34, 77.88 (6×C-3), 82.01, 82.12, 83.12, 83.58, 83.66 (6×C-2), 170.33, 170.49, 170.79, 170.82, 171.99 (6×C═O).

4.1.6. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonate 20. Triethylsilyl trifluoromethanesulfonate (0.17 mL, 0.75 mmol) was added to a stirred solution of tetramer **15** (19 mg, 0.03 mmol) in pyridine (0.5 mL) at −20 °C. The reaction mixture was allowed to warm to room temperature over 6 h. After 14 h, TLC (ethyl acetate–pet. ether, 3:1) showed some starting materials (R_f 0.0) and the presence of a major product (R_f 0.2). The reaction mixture was concentrated in vacuo and purified by flash chromatography on basic alumina (ethyl acetate–pet. ether, 3:1) to yield the silylated tetramer **20** (4 mg, 13%) as a colourless oil: $[\alpha]_D^{24}$ −23.4 (*c* 0.47 in $CHCl_3$); Isotope distribution *m/z* (ES+ve) found: 1059.53 (100), 1060.48 (80), 1061.55 (43), 1062.44 (18), 1063.38 (9%). $C_{47}H_{91}N_6O_{13}Si_4$ ($M+H^+$) requires: 1059 (100), 1060 (75), 1061 (44), 1062 (18), 1063 (6%); ν_{max} (thin film): 3410 (NH), 2105 (N_3), 1740 (C═O), 1637, 1540 (C═O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 0.61–0.71 (24H, m, 4×Si(CH_2CH_3)$_3$), 0.92–0.98 (36H, m, 4×Si(CH_2CH_3)$_3$), 1.26–1.30 (6H, m, $CH(CH_3)_2$), 3.78–3.80 (3H, m, H-5^B, H-5^C and H-5^D), 3.92–3.96 (2H, m, H-4^A and H-5^A), 4.16–4.21 (3H, m, H-4^B, H-4^C and H-4^D), 4.27 (1H, dd, $J_{5'A,4A}$ 4.1, $J_{5A,5'A}$ 9.5, H-$5'^A$), 4.30–4.40 (5H, m, H-2^C, H-2^D, H-$5'^B$, H-$5'^C$ and H-$5'^D$), 4.43–4.46 (2H, m, H-2^B and H-3^A), 4.48–4.49 (2H, m, H-3^C and H-3^D), 4.52–4.55 (2H, m, H-2^A and H-3^B), 5.07 (1H, sept, *J* 6.2, $CH(CH_3)_2$), 6.52 (1H, d, *J* 6.7, NH^D), 6.55 (1H, d, *J* 6.7, NH^C), 6.60 (1H, d, *J* 6.4, NH^B); δ_C ($CDCl_3$, 125.7 MHz) 4.66, 4.68, 4.76 (4×Si(CH_2CH_3)$_3$), 6.83, 6.90 (4×Si(CH_2CH_3)$_3$), 22.10, 22.17 ($CH(CH_3)_2$), 57.71, 57.74 (3×C-4), 67.53 (C-4^A), 68.99 ($CH(CH_3)_2$), 71.59, 71.86, 72.33, 72.45 (4×C-5), 76.78, 77.43, 77.88 (4×C-3), 81.47, 82.54, 82.56, 82.64 (4×C-2), 168.60 (C═O^A), 168.77 (C═O^B), 169.00, 169.02 (C═O^D and C═O^C); *m/z* (APCI+ve) 156 (100), 1059 ($M+H^+$, 95%).

Acknowledgements

Support from the EPSRC (A.A.E.) and DST, New Delhi, for a BOYCAST Fellowship (G.J.S.) is gratefully acknowledged.

References and notes

1. Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969–977.
2. Hamman, J. H.; Enslin, G. M.; Kotze, A. F. *Biodrugs* **2005**, *19*, 165–177.
3. Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963–978.
4. Potocky, T. B.; Menon, A. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 3686–3687.
5. Lagenham, J. M.; Gellman, S. H. *Org. Lett.* **2004**, *6*, 937–940.
6. Park, J.; Lee, H.; Lai, J. R.; Kim, B. M.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 8539–8545.
7. Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324–7330.
8. Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
9. Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445–455.
10. Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111–1239.
11. Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, *9*, 1127–1153.
12. Smith, M. D.; Fleet, G. W. J. *J. Pept. Sci.* **1999**, *5*, 425–441.
13. Bertelli, A.; Donati, L.; Lami, V.; Prino, G.; Rossano, M. A. *Int. J. Neuropharmacol.* **1968**, *7*, 149–154.
14. Friestad, G. K.; Marie, J. C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249–3252.
15. Hagihara, M.; Anthony, T. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568–6570.
16. Reetz, M. T.; Griebenow, N.; Goddard, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1605–1606.
17. Grison, C.; Geneve, S.; Claudel, S.; Coutrol, P.; Marraud, M. *Tetrahedron Lett.* **2003**, *44*, 2297–2300.

18. Seebach, D.; Beck, A. K.; Brenner, M.; Gaul, C.; Heckel, A. *Chimia* **2001**, *55*, 831–838.
19. Baldauf, C.; Gunther, R.; Hofmann, H.-J. *J. Org. Chem.* **2005**, *70*, 5351–5361.
20. Brenner, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 2155–2166.
21. Hanessian, S.; Luo, X.; Schaum, R. *Tetrahedron Lett.* **1999**, *40*, 4925–4929.
22. Seebach, D.; Schaeffer, L.; Brenner, M.; Hoyer, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 776–778.
23. Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011.
24. Allan, R. D.; Tran, H. W. *Aust. J. Chem.* **1984**, *37*, 1123–1126.
25. Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077–11078.
26. Schweizer, F.; Otter, A.; Hindsgaul, O. *Synlett* **2001**, 1743–1746.
27. Xiao, D.; Carroll, P. J.; Mayer, S. C.; Pfizenmayer, A. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3043–3046.
28. Carballido, M.; Castedo, L.; Gonzalez-Bello, C. *Eur. J. Org. Chem.* **2004**, 3663–3668.
29. Crisma, M.; Moretto, A.; Toniolo, C.; Kaczmarek, K.; Zabrocki, J. *Macromolecules* **2001**, *34*, 5048–5052.
30. Farrera-Sinfreu, J.; Zaccaro, L.; Vidal, D.; Salvatella, X.; Giralt, E.; Pons, M.; Albericio, F.; Royo, M. *J. Am. Chem. Soc.* **2004**, *126*, 6048–6057.
31. Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277–4280.
32. Mouries, C.; Deguin, B.; Lamari, F.; Foglietti, M. J.; Tillequin, F.; Koch, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1083–1086.
33. Jensen, K. J.; Brask, J. *Biopolymers* **2005**, *80*, 747–761.
34. Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *Glycoconj. J.* **2005**, *22*, 83–93.
35. Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *118*, 187–207.
36. Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514.
37. Chakraborty, T. K.; Reddy, V. R.; Sudhakar, G.; Kumar, S. U.; Reddy, T. J.; Kumar, S. K.; Kunwar, A. C.; Mathur, A.; Sharma, R.; Gupta, N.; Prasad, S. *Tetrahedron* **2004**, *60*, 8329–8339.
38. Grotenbreg, G. S.; Timmer, M. S. M.; Llamas-Saiz, A. L.; Verdoes, M.; van der Marel, G. A.; van Raaij, M.; Overkleeft, H. S.; Overhand, M. *J. Am. Chem. Soc.* **2004**, *126*, 3444–3446.
39. van Well, R. M.; Overkleeft, H. S.; van der Marel, G. A.; Bruss, D.; Thibault, G.; de Groot, P. G.; van Boom, J. H.; Overhand, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 331–334.
40. Edwards, A. A.; Fleet, G. W. J.; Tranter, G. E. *Chirality* **2006**, *18*, 265–272.
41. Johnson, S. W.; Jenkinson (nee Barker), S. F.; Perez-Victoria, I.; Edwards, A.; Claridge, T. D. W.; Tranter, G.; Fleet, G. W. J.; Jones, J. H. *J. Pept. Sci.* **2005**, *11*, 517–524.
42. Claridge, T. D. W.; Long, D. D.; Baker, C. M.; Odell, B.; Grant, G. H.; Edwards, A. A.; Tranter, G. E.; Fleet, G. W. J.; Smith, M. D. *J. Org. Chem.* **2005**, *70*, 2082–2090.
43. Smith, M. D.; Claridge, T. D. W.; Sansom, M. S. P.; Fleet, G. W. J. *Org. Biomol. Chem.* **2003**, *1*, 3647–3655.
44. Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stockle, M.; Kessler, H. *Chem.—Eur. J.* **2002**, *8*, 4365–4376.
45. Edwards, A. A.; Ichihara, O.; Murfin, S.; Wilkes, R.; Whittaker, M.; Watkin, D. J.; Fleet, G. W. J. *J. Comb. Chem.* **2004**, *6*, 230–238.
46. Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802–2803.
47. Sanjayan, G.; Stewart, A.; Hachisu, S.; Gonzalez, R.; Watterson, M. P.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5847–5852.
48. Watterson, M. P.; Edwards, A. A.; Leach, J. A.; Smith, M. D.; Ichihara, O.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5853–5857.
49. Edwards, A. A.; Sanjayan, G. J.; Hachisu, S.; Soengas, R.; Stewart, A.; Tranter, G. E.; Fleet, G. W. J. *Tetrahedron* **2006**, *62*, 4110–4119.
50. Milner-White, E. J.; Ross, B. M.; Ismali, R.; Belhadj-Mostefa, K.; Poet, R. *J. Mol. Biol.* **1988**, *204*, 777–782.
51. Milner-White, E. J. *J. Mol. Biol.* **1990**, *216*, 385–397.
52. Guruprasad, K.; Rajkumar, S. *J. Biosci.* **2000**, *25*, 143–156.
53. Guruprasad, K.; Shukla, S.; Adindla, S.; Guruprasad, L. *J. Pept. Res.* **2003**, *61*, 243–251.
54. Kaur, H.; Raghava, G. P. S. *Protein Sci.* **2003**, *12*, 923–929.
55. Etzkorn, F. A.; Travins, J. M.; Hart, S. A. *Adv. Amino Acid Mimetics Peptidomimetics* **1999**, *2*, 125–163.
56. Lindvall, M. K.; Rissanen, K.; Hakala, J. M. L.; Koskinen, A. M. P. *Tetrahedron Lett.* **1999**, *40*, 7427–7430.
57. Belvisi, L.; Gennari, C.; Mieglo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 389–400.
58. Curran, T. P.; Chandler, N. M.; Kennedy, R. J.; Keaney, M. T. *Tetrahedron Lett.* **1996**, *37*, 1933–1936.
59. Ramanathan, S. K.; Keeler, J.; Lee, H. L.; Reddy, D. S.; Lushington, G.; Aube, J. *Org. Lett.* **2005**, *7*, 1059–1062.
60. Jimenez, A. I.; Ballano, G.; Cativiela, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 396–399.
61. Sato, M.; Lee, J. Y. H.; Nakanashi, H.; Johnson, M. E.; Chruschiel, R. A.; Kahn, M. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 999–1006.
62. Brickmann, K.; Yuan, Z.; Sethson, I.; Somfai, P.; Kihlberg, J. *Chem.—Eur. J.* **1999**, *5*, 2241–2253.
63. Schmidt, B.; Lindman, S.; Tong, W.; Lindeberg, G.; Gogoll, A.; Lai, Z.; Thoernwall, M.; Synnergren, B.; Nilsson, A.; Welch, C. J.; Sohtell, M.; Westerlund, C.; Nyberg, F.; Karlen, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 903–919.
64. Yang, D.; Li, W.; Qu, J.; Luo, S.-W.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 13018–13019.
65. Schumann, F.; Mueller, A.; Koksch, M.; Mueller, G.; Sewald, N. *J. Am. Chem. Soc.* **2000**, *122*, 12009–12010.
66. Brittain, D. E. A.; Watterson, M. P.; Claridge, T. D. W.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655–3665.
67. Humphreys, S.; Watkin, D. J.; Sanjayan, G.; Tranter, G.; Edwards, A.; Fleet, G. W. J. *Acta Crystallogr., Sect. E.—Struct. Rep. Online* **2005**, *E61*, o918–o919.