Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3263–3273

Pseudoenantiomeric oxetane δ-amino acid scaffolds derived from L-rhamnose and D-xylose: D/L-alanine-D-serine and glycine-L-serine dipeptide isosteres

Stephen W. Johnson, Sarah. F. Jenkinson (née Barker), Donald Angus, John H. Jones, David J. Watkin and George W. J. Fleet*

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

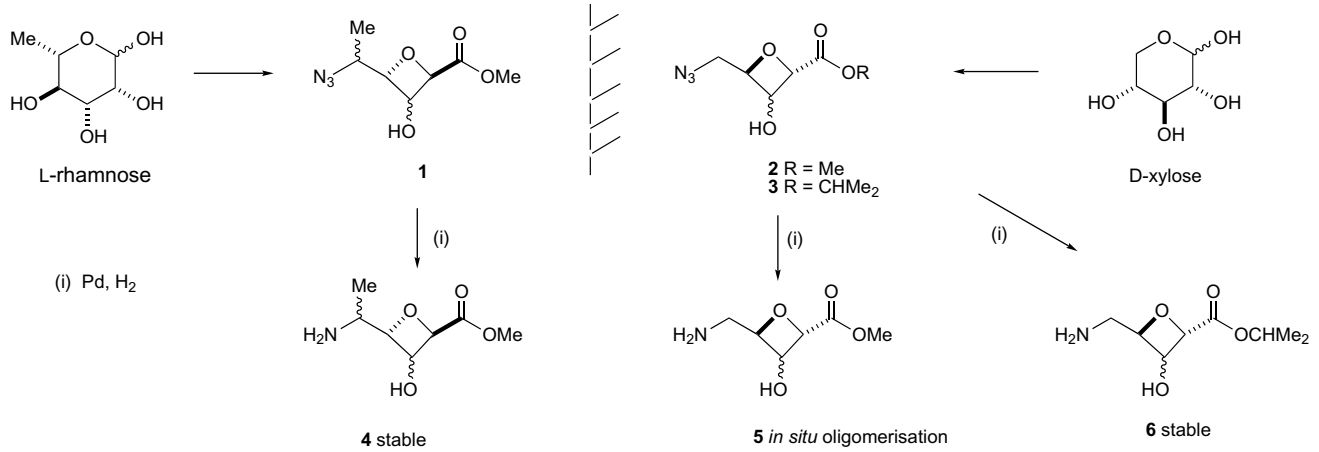
Received 26 July 2004; accepted 20 August 2004
Available online 1 October 2004

Abstract—A series of oxetane δ-amino acid scaffolds derived from L-rhamnose and D-xylose provide a new class of templated sugar amino acids (SAA), which can be considered as D/L-alanine-D-serine and glycine-L-serine dipeptide isosteres.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

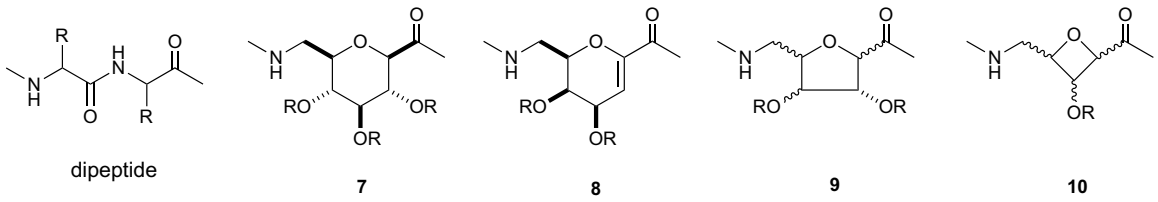
The preparations of the diastereomers of **1** from L-rhamnose and of the pseudoenantiomeric esters **2** and **3** from D-xylose provide oxetane δ-amino acid scaffolds suitable for incorporation as peptidomimetics. On hydrogenation, methyl esters **1** form amines **4** (in which the primary amine is attached to a secondary carbon), which are stable enough to use as building blocks. However, the corresponding methyl esters **2** give amines **5**, which tend to oligomerise. For the use of these building blocks, it is therefore necessary to use the more hindered isopropyl esters **3** allowing access to amines **6** as stable synthetic intermediates.

Sugar amino acids (SAAs) constitute an important class of peptidomimetics in both their potential as library building blocks[1] and their innate predisposition to induce novel secondary structures.[2] In particular, it is well established that δ-SAAs can act as conformationally restricted dipeptide isosteres. Saturated **7**[3] and unsaturated **8**[4] pyranose and furanose **9**[5] SAA scaffolds have been extensively studied but there are no previous reports of the corresponding oxetanose derivatives **10**.



* Corresponding author. E-mail: george.fleet@chem.ox.ac.uk

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.08.023



L-Rhamnose may be efficiently converted into the benzylidene acetal **12**,[6,7] a key intermediate for the preparation of a series of oxetane β-amino acids (Scheme 1).[8] Introduction of an azide functionality with retention of configuration at C-5 of **12** provided scaffolds **11** and **14**, both of which may be viewed as conformationally restricted mimetics of L-alanine-D-serine; in contrast, when the nitrogen function was introduced with an inversion of configuration in **12**, the D-alanine-D-serine scaffolds **13** and **15** were accessible.

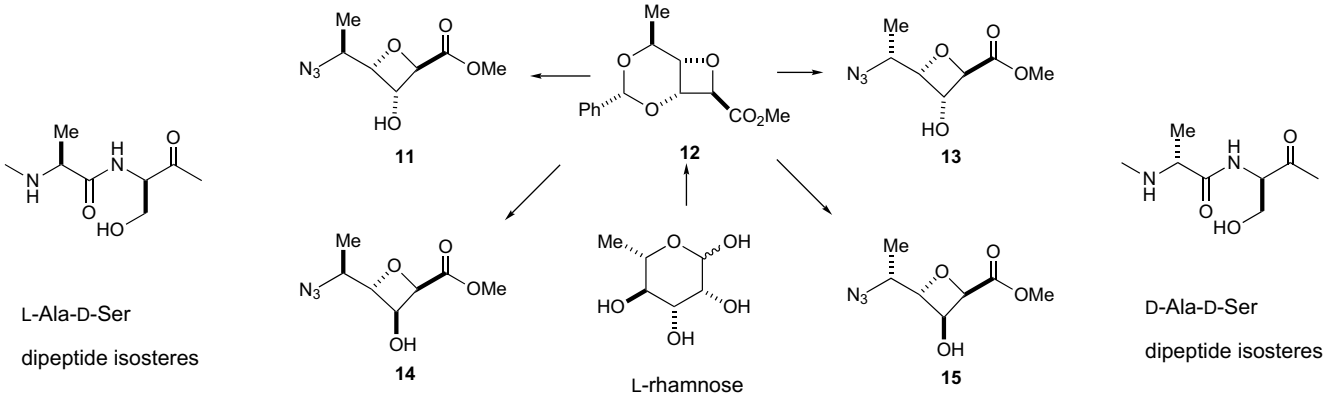
The approach to the pseudoenantiomeric scaffolds for Gly-L-Ser **17** and **18** relied on a short and efficient synthesis of the benzylidene oxetane **16** from D-xylose,[9,10] which may be further elaborated to the target building blocks (Scheme 2).

The synthetic strategy described herein of using acetal protection, limits the targets to oxetane scaffolds, which have the C-2 and C-4 carbon substituents *trans* to each other. This is the consequence of the shortest sequences for the synthesis of oxetane carboxylates from sugar lactones requiring a *cis* relationship between the efficient protection of C-3 and C-5 OH groups of the incipient oxetane as an acetal. All efficient ring contractions of sugar triflates α- to the lactone carbonyl result in the C-2 carboxylate being *trans* to the C-3 oxygen.[6] In the case of δ-amino acids containing a THF ring, secondary structural features are usually established in short homooligomers from 2,5-*cis* substituted THF SAAs;[11] in contrast there is only one case where a 2,5-*trans* substituted THF SAA gives rise to a helical structure.[12] A different [and more lengthy] protecting group strategy to that used in the present work is required for the synthesis of *cis*-2,4-disubstituted oxetanes.

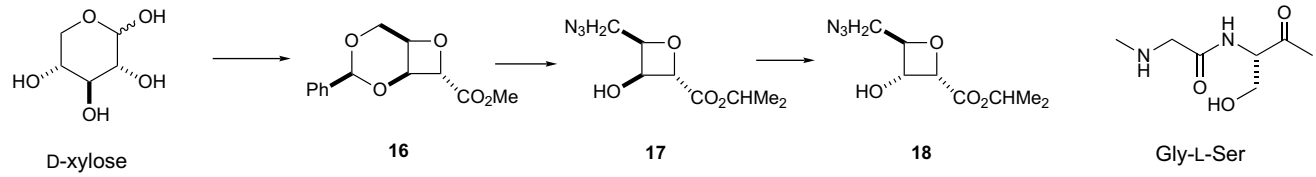
2. Results and discussion

2.1. Synthesis of D/L-Ala-D-Ser oxetane dipeptide isosteres from L-rhamnose

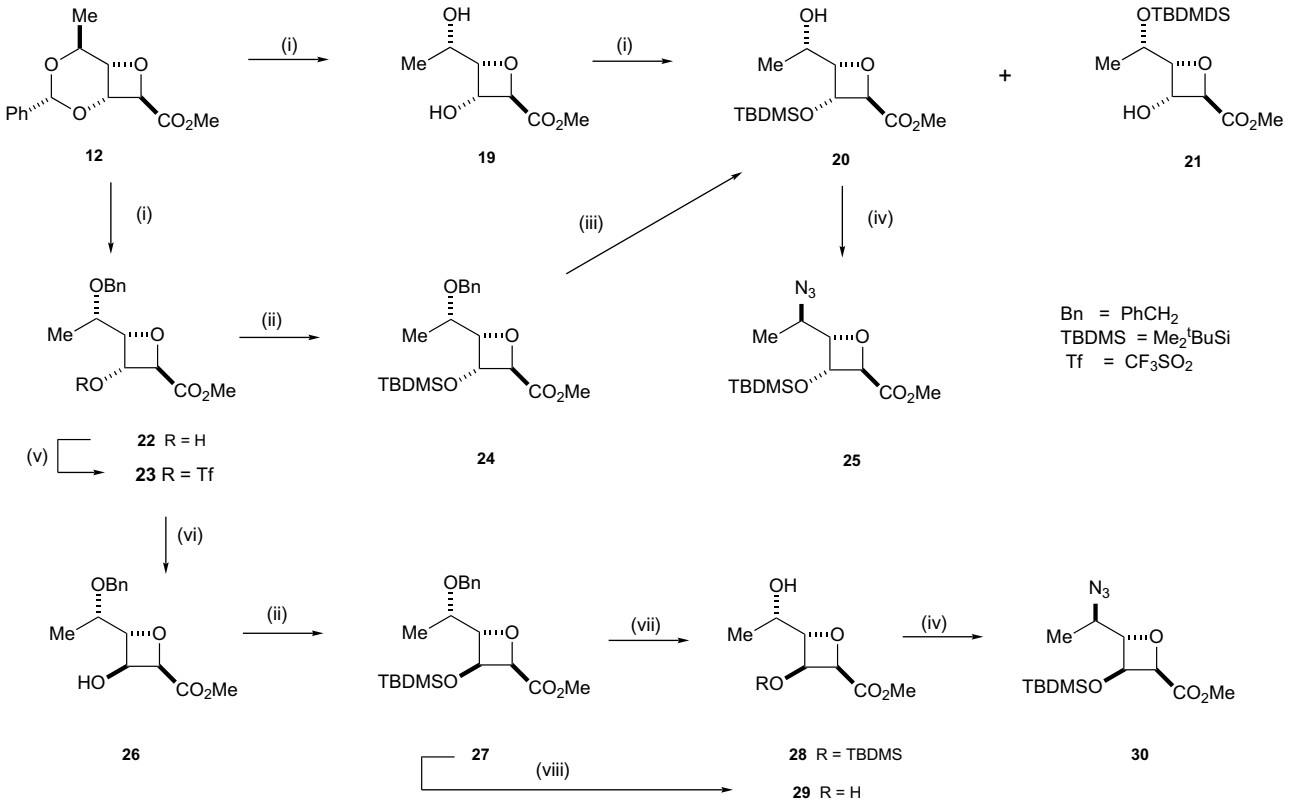
For the preparation of D-Ala-D-Ser scaffolds, it is necessary to introduce a nitrogen function at C-5 of L-rhamnose with a single inversion of configuration. While aqueous hydrolysis of **12** gave diol **19** in good yield, attempts to discriminate between the C-3 and C-5 hydroxyl groups were unsuccessful (Scheme 3). The reaction



Scheme 1. D/L-Alanine-D-serine dipeptide isosteres derived from L-rhamnose.



Scheme 2. Glycine-L-serine dipeptide isosteres derived from D-xylose.



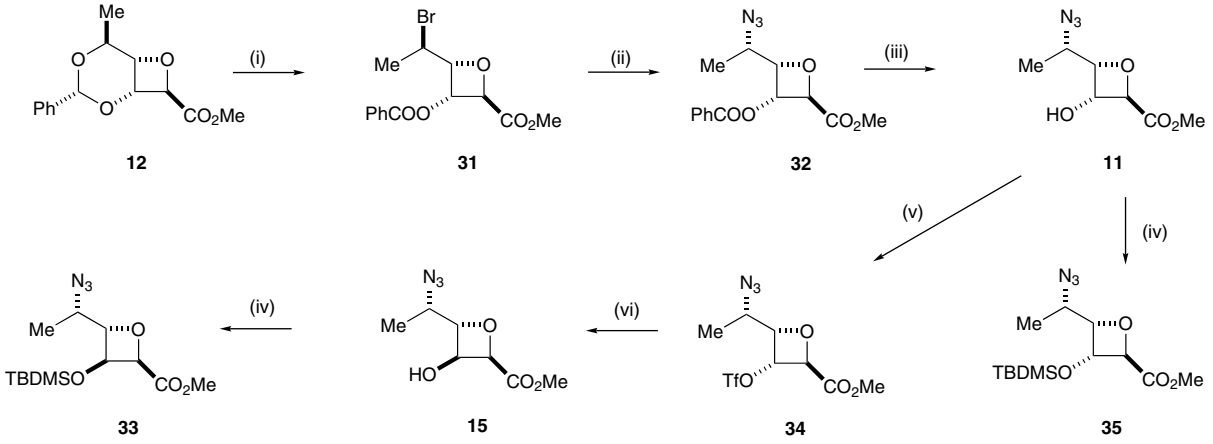
Scheme 3. Reagents and conditions: (i) see text and Ref. 7; (ii) *tert*-$BuMe_2SiOSO_2CF_3$, pyridine, CH_2Cl_2; (iii) H_2, Pd black, MeOH; (iv) Ph_3P, $EtO_2CN{=}NCO_2Et$, DPPA, THF; (v) Tf_2O, pyridine, CH_2Cl_2; (vi) CF_3CO_2Cs, MeCOEt; (vii) H_2, Pd black, MeOH; (viii) H_2, Pd black, dioxane.

of **19** with TBDMS chloride and TBDMS triflate under a variety of conditions gave approximately a 1:1 mixture of the two monosilyl derivatives **20** and **21**, which were difficult to separate (Scheme 3). It is clear that such a procedure was not a feasible way to make large quantities of **20** meaning that a different strategy had to be employed.

Reduction of the benzylidene acetal **12** with triethylsilane in the presence of triflic acid[13] gave a highly regioselective reductive cleavage to form the 5-*O*-benzyl ether **22** in 82% yield;[7] this efficient procedure allowed **22** to be the key intermediate for the D-Ala-D-Ser building blocks. Treatment of alcohol **22** with TBDMS triflate gave silyl ether **24** (97% yield), which on hydrogenation in the presence of palladium black in methanol afforded L-rhamnonate **20** (99% yield) in which only the C-5 hydroxyl group is unprotected. A Mitsunobu reaction of the L-rhamnonate **20** with diphenylphosphorylazide (DPPA), triphenylphosphine and diethyl azodicarboxylate (DEAD) introduced an azide at C-5 with a single inversion to give the required D-gulonate **25** in 70% yield. The overall yield of TBDMS protected 2,3-*trans*-D-Ala-D-Ser dipeptide scaffold **25** from the benzyl ether **22** was 67%.

Inversion of the configuration of the hydroxyl group in the oxetane ring by an efficient S_N2 reaction allows access to the 2,3-*cis*-D-Ala-D-Ser dipeptide scaffold **30**. Esterification of alcohol **22** with trifluoromethanesulfonic (triflic) anhydride in dichloromethane in the presence of pyridine to the corresponding triflate **23** (98% yield), and subsequent treatment with caesium trifluoroacetate in butanone, gave L-altronate **26** in 95% yield. Reaction of **26** with TBDMS triflate afforded silyl ether **27** (95% yield), which on hydrogenolysis of the benzyl ether in dioxane gave access to alcohol **28** (99% yield); hydrogenolysis in methanol was accompanied by substantial loss of the silyl protecting group to give **29**. Introduction of an azide function in **28** by the Mitsunobu reaction formed the 2,3-*cis*-D-Ala-D-Ser dipeptide scaffold **30** (91% yield) in an overall yield of 80% from **22** (Scheme 3).

The introduction of a nitrogen function at C-5 of L-rhamnose with two inversions of configuration was required for the generation of the L-Ala-D-Ser scaffolds (Scheme 4). Bromination of benzylidene oxetane **12** by *N*-bromosuccinimide (NBS) in the presence of barium carbonate (Hanessian–Hullar conditions[14]) gave a highly regioselective ring opening with an initial inversion at C-5 to form bromobenzoate **31** in 86% yield. Reaction of bromide **31** with sodium azide in DMSO proceeded with a second inversion at C-5 to give the azidorhamnonate **32** in 65% yield. Attempts to remove the benzoate protecting group in **32** by transesterification with methoxide resulted in a retro-aldol reaction of the product (this reaction is discussed in more detail in regard to the xylose-derived azidoesters below); accordingly both the ester functionalities in **32** were hydrolysed with aqueous sodium hydroxide in tetrahydrofuran with the resulting sodium salt treated with methanolic



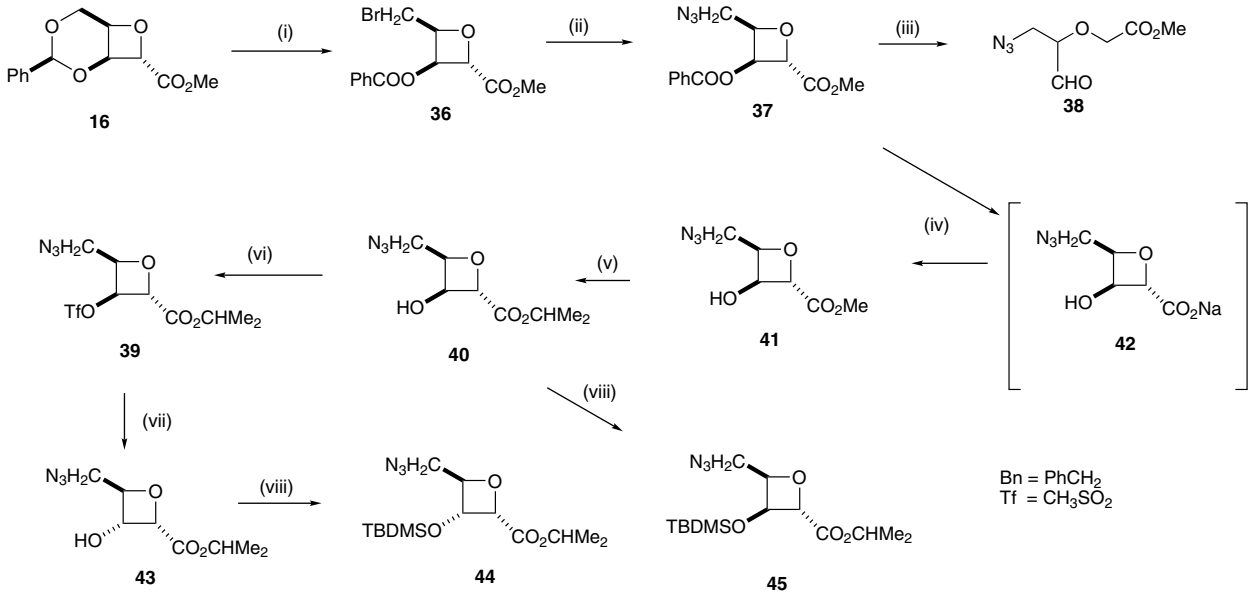
Scheme 4. Reagents and conditions: (i) NBS, $BaCO_3$, CCl_4; (ii) NaN_3, DMSO; (iii) NaOH, H_2O, THF; then HCl, MeOH; (iv) *tert*-$BuMe_2SiOSO_2CF_3$, pyridine, CH_2Cl_2; (v) Tf_2O, pyridine, CH_2Cl_2; (vi) CF_3CO_2Cs, MeCOEt.

hydrogen chloride to form the deprotected azidoester **11**, in which the OH at C-3 is *trans* to the C-2 carboxylate, **11** (89% yield). Reaction of alcohol **11** with TBDMS triflate gave the target azidorhamnonate **35** (87% yield; 43% overall yield from **12**).

The azido-L-altronate **15**, with the OH at C-3 *cis* to the C-2 carboxylate, was prepared by an efficient S_N2 displacement of the triflate at C-3 of the oxetane ring in **11**. Esterification of the rhamnonate alcohol **11** with triflic anhydride gave the corresponding triflate **34** (100% yield), which on treatment with caesium trifluoroacetate in butanone gave the altronate alcohol **15** (99% yield). The structure of azidoalcohol **15**, which from L-rhamnose involved five highly efficient inversions of configuration—two S_N2 displacements at C-5, a double inversion at C-2 and a single inversion at C-3—was firmly established by X-ray crystallographic analysis.[15] Further treatment of alcohol **15** with TBDMS triflate afforded the target 2,3-*cis*- L-Ala-D-Ser dipeptide scaffold **33** (99% yield).

2.2. Synthesis of oxetane dipeptide isosteres from D-xylose

The benzylidene oxetane **16** (derived from D-xylose) with NBS in carbon tetrachloride in the presence of barium carbonate gave the bromobenzoate **36** in 81% yield as previously described (Scheme 5).[9] Reaction of bromide **36** with sodium azide in DMF produced azide **37** (89% yield). Attempts to remove the benzoate ester function in **37** by transesterification were unsuccessful; treatment of **37** with sodium methoxide in methanol gave a number of products, at least some of which arose from a reverse aldol reaction following ester exchange of the benzoate. The major product isolated in 37% yield had IR and NMR spectra consistent with the structure shown for **38**. The base-catalysed reverse aldol could



Scheme 5. Reagents and conditions: (i) NBS, $BaCO_3$, CCl_4; (ii) NaN_3, DMF; (iii) NaOMe, MeOH; (iv) NaOH, H_2O, THF; then MeOH, HCl; (v) Me_2CHOH, *p*-TSA; (vi) Tf_2O, CH_2Cl_2, pyridine; (vii) CF_3COOCs, MeCOEt; (viii) *tert*-$BuMe_2SiOSO_2CF_3$, pyridine, CH_2Cl_2.

be avoided by aqueous hydrolysis of both esters with aqueous sodium hydroxide; the resultant sodium salt **42** with hydrogen chloride in methanol afforded methyl ester **41** (90% yield). Reaction of methyl ester **41** with *p*-TSA in isopropanol resulted in transesterification to the isopropyl ester **40** (88% yield), which on treatment with TBDMS triflate gave the 2,3-*trans*-Gly-L-Ser dipeptide scaffold **45** (98% yield) (Scheme 5).

Scaffold **44** in which the C-3 oxygen is *cis* to the carboxylate was prepared from **40** by conversion to triflate **39** (96% yield), after which an efficient S_N2 displacement by caesium trifluoroacetate in butanone afforded the inverted alcohol **43** (98% yield). Finally protection of alcohol **43** by treatment with TBDMS triflate gave the target scaffold **44** in 48% yield.

3. Conclusion

A series of dipeptide isosteres based on oxetane δ-amino acid scaffolds were prepared in short efficient sequences from L-rhamnose and D-xylose by a series of highly regioselective reactions and S_N2 displacements. The scaffolds from L-rhamnose may be viewed as L-Ala-D-Ser and D-Ala-D-Ser and dipeptide isosteres; they may also be viewed as isosteres for D/L-Ala-D-lactate. The use of acetals for protection in the construction of the oxetane ring provided high yield short sequences but has the consequence that all the amino acids described have the carbon chain at C-4 of the oxetane ring *trans* to the carboxylate at C-2. A lengthier sequence with a different protecting group strategy, which allows the synthesis of oxetanes in which the C-2 and C-4 chains of the oxetane are *cis* to each other, together with the synthesis of homooligomers of oxetane δ-amino acids and studies on their secondary structures,[16] will be reported in due course.

4. Experimental

Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over dried 3 Å molecular sieves; hexane refers to 60–80 °C petroleum ether; water was distilled. *N*,*N*-Dimethylformamide was purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed under an atmosphere of nitrogen or hydrogen gas were maintained by an inflated balloon. pH 7 Buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). All other reagents were used as supplied, without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Köfler hot block and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 500 or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) or where stated on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform, or Perkin–Elmer Paragon 1000 spectrophotometer using thin films on NaCl plates (thin film). Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded using the following techniques: electrospray ionisation (ES), chemical ionisation (CI, NH_3), or atmospheric pressure chemical ionisation (APCI). ES mass spectra were measured on a Micromass BioQ II-ZS mass spectrometer. CI mass spectra were recorded on a Micromass 500 OAT spectrometer. APCI mass spectra were recorded on a Micromass Platform 1 mass spectrometer via an 'Openlynx' system. High resolution mass spectra (HRMS) were recorded on a Micromass 500 OAT spectrometer by chemical ionisation (CI, NH_3) or a Waters 2790-Micromass LCT mass spectrometer by electrospray ionisation (ES) as stated. For ES mass spectra the spectrometer was operated at a resolution of 5000 full width half height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly-DL-alanine with Leu-enkephalin as the internal lock mass. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL.

4.1. Methyl 2,4-anhydro-5-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-L-rhamnonate 24

TBDMS triflate (0.87 mL, 3.8 mmol) was added dropwise to a stirred solution of the benzyl protected L-rhamnonate **22**[7] (0.506 g, 1.90 mmol) and pyridine (0.61 mL, 7.6 mmol) in dichloromethane (12 mL) at −20 °C under nitrogen. The reaction mixture was allowed to stir for 20 min at −20 °C, then warmed to 0 °C. After 2 h, TLC (1:1, EtOAc/hexane) indicated the formation of a single major product (R_f 0.64) and the absence of starting material (R_f 0.40). The solution was diluted with dichloromethane (100 mL), washed with water (23 mL), dried over magnesium sulfate, filtered and the solvent removed. The residue was purified by flash chromatography (1:1, EtOAc/hexane) to give silyl ether **24** (0.70 g, 97%) as a clear oil. Found: C, 63.10; H, 8.47; $C_{20}H_{32}O_5Si$ requires: C, 63.12; H, 8.48; $[\alpha]_D^{22} = +33.5$ (c, 1.25 in Me_2CO); ν_{max} (NaCl) 2858–2954 (C–H), 1737, 1758 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.05, 0.09 (2 × s, 2 × 3H, SiMe_2), 0.92 (s, 9H, Si^t*Bu*), 1.33 (d, 3H, H-6, J 6.4), 3.82 (s, 3H, –CO_2Me), 4.18 (dq, 1H, H-5, $J_{4,5} \approx J_{5,6} \approx 6.5$), 4.51 (d, 1H, PhC$H_2$O–, J_{GEM} 11.6), 4.62 (d, 1H, PhCH_2O–, J_{GEM} 11.6), 4.70 (dd, 1H, H-4, J 7.0, 5.8), 4.82–4.86 (m, 2H, H-2, H-3), 7.29–7.35 (m, 5H, Ph); δ_C ($CDCl_3$, 100.6 MHz): −4.66 (–Si(CH_3)$_2$), 15.13 (C-6), 18.44 (–SiCMe_3), 26.14 (SiC(CH_3)$_3$), 52.62 (–CO_2CH_3), 70.55 (C-2 or C-3), 70.84 (PhCH_2O–), 72.84 (C-5), 86.20

(C-2 or C-3), 87.84 (C-4), 127.84–128.70 (Ph), 139.15 (C_{IPSO}), 171.54 (C-1).

4.2. Methyl 2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-L-rhamnonate 20

A solution of benzyl ether **24** (0.345 g, 0.907 mmol) in methanol (2.35 mL) was stirred under hydrogen in the presence of palladium black (0.035 g). After 17 h, TLC (1:1, EtOAc/hexane) indicated the presence of one product (R_f 0.55) and no starting material. The reaction mixture was degassed, flushed with nitrogen and then filtered through Celite®. The solvent was removed to give silyl ether **20** (0.262 g, 99% yield) as a clear oil. Found: C, 53.82; H, 9.06; $C_{13}H_{26}O_5Si$ requires: C, 53.76; H, 9.02; $[\alpha]_D^{23} = +26.6$ (*c*, 0.70 in Me_2CO); ν_{max} (NaCl) 3532 (O–H), 2931 (C–H), 1757 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.12, 0.14 (2 × s, 2 × 3H, Si*Me*$_2$), 0.92 (s, 9H, Si^t*Bu*), 1.24 (d, 3H, H-6, *J* 6.4), 2.64 (d, 1H, –O*H*, *J* 0.4), 3.82 (s, 3H, –CO_2*Me*), 4.29–4.35 (m, 1H, H-5), 4.39 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 7.0$), 4.89 (dd, 1H, H-3, *J* 6.4, 5.2), 4.96 (d, 1H, H-2, *J* 5.2); δ_C ($CDCl_3$, 100.6 MHz): −5.55, −4.85 (–Si(*C*H$_3$)$_2$), 17.70, 18.06 (C-6, –Si*C*Me$_3$), 25.56 (SiC(*C*H$_3$)$_3$), 52.25 (–CO_2*C*H$_3$), 67.02 (C-5), 70.22 (C-3), 85.30 (C-2), 86.63 (C-4), 170.67 (C-1).

4.3. Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate 25

A solution of silyl ether **20** (0.117 g, 0.403 mmol) and triphenylphosphine (0.212 g, 0.806 mmol) in tetrahydrofuran (5.2 mL) was prepared and stirred under nitrogen at 0 °C in the dark. Diethyl azodicarboxylate (0.127 mL, 0.806 mmol) was added dropwise, then DPPA (0.087 mL, 0.403 mmol) added dropwise. After 15 min, the solution was allowed to warm to room temperature. After 18 h, TLC (1:2, EtOAc/hexane) revealed the formation of a major product (R_f 0.50). The solvent was removed and the residue purified by repeated flash chromatography (1:3, EtOAc/hexane), to give the 2,3-*trans*-D-Ala-D-Ser dipeptide scaffold **25** (0.090 g, 70%) as a white crystalline solid. Found: C, 49.91; H, 8.25; N, 13.15; $C_{13}H_{25}N_3O_4Si$ requires: C, 49.50; H, 7.99; N, 13.32; HRMS *m*/*z* (CI+): found 316.1690 (MH^+), $C_{13}H_{26}N_3O_4Si$ requires 316.1693; mp 29–30 °C; $[\alpha]_D^{25} = +10.4$ (*c*, 0.96 in $CHCl_3$); ν_{max} (NaCl) 2859–2955 (C–H), 2093 (N_3), 1739, 1759 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.08, 0.11 (2 × s, 2 × 3H, Si*Me*$_2$), 0.92 (s, 9H, Si^t*Bu*), 1.16 (d, 3H, H-6, *J* 6.7), 3.82 (s, 3H, –CO_2*Me*), 4.06 (dq, 1H, H-5, *J* 8.2, 6.7), 4.55 (ddd, 1H, H-4, *J* 8.2, 6.3, 0.7), 4.79 (dd, 1H, H-3, *J* 4.9, 6.3), 4.96 (dd, 1H, H-2, *J* 4.9, 0.7); δ_C ($CDCl_3$, 100.6 MHz): −5.44, −4.85 (–Si(*C*H$_3$)$_2$), 15.47 (C-6), 17.83 (–Si*C*Me$_3$), 25.56 (SiC(*C*H$_3$)$_3$), 52.22 (–CO_2*C*H$_3$), 57.08 (C-5), 69.44 (C-3), 85.59 (C-2), 87.82 (C-4), 170.58 (C-1); MS (ESI+) *m*/*z*: 338.06 (MNa^+, 100%).

4.4. Methyl 2,4-anhydro-5-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-L-rhamnonate 23

Triflic anhydride (0.442 mL, 2.696 mmol) was added dropwise to a solution of pyridine (0.544 mL, 6.74 mmol) and alcohol **22** (0.359 g, 1.348 mmol) in dichloromethane (5.4 mL) under nitrogen at −78 °C; the mixture was stirred at −78 °C for a further 20 min, before warming to 0 °C. After 3 h, TLC (1:1, EtOAc/hexane) revealed that the starting material (R_f 0.46) had been completely replaced by one product (R_f 0.65). At this point, the reaction mixture was diluted with dichloromethane (40 mL), washed with 0.1 M aqueous hydrochloric acid (20 mL) and then water (20 mL). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography (2:3, EtOAc/hexane) to give triflate **23** (0.519 g, 97% yield) as a clear oil. Found: C, 45.48; H, 4.28; $C_{15}H_{17}F_3O_7S$ requires: C, 45.23; H, 4.30; $[\alpha]_D^{26} = +13.1$ (*c*, 1.64 in $CHCl_3$); ν_{max} (NaCl) 2873–3040 (C–H), 1760 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.31 (d, 3H, H-6, *J* 6.2), 3.87 (s, 3H, CO_2*Me*), 4.16 (dq, 1H, H-5, *J* 8.4, 6.2), 4.56 (d, 1H, PhC*H*, J_{GEM} 10.8), 4.64 (d, 1H, PhC*H*′, J_{GEM} 10.8), 4.75 (ddd, 1H, H-4, *J* 8.4, 6.1, 1.2), 5.16 (dd, 1H, H-2, *J* 4.6, 1.2), 5.72 (dd, 1H, H-3, *J* 6.1, 4.6), 7.28–7.36 (m, 5H, Ph); δ_C ($CDCl_3$, 100.6 MHz): 14.60 (C-6), 53.01 (CO_2CH_3), 70.77 (Ph*C*H$_2$), 72.08 (C-5), 79.29 (C-3), 81.14 (C-2), 84.36 (C-4), 127.77, 127.91, 128.37 (Ph), 137.64 (C_{IPSO}), 168.17 (C-1); MS (APCI+) *m*/*z*: 416.00 (MNH_4^+, 100%).

4.5. Methyl 2,4-anhydro-5-*O*-benzyl-6-deoxy-L-altronate 26

Caesium trifluoroacetate (0.970 g, 3.909 mmol) was added to a solution of triflate **23** (0.519 g, 1.303 mmol) in butanone (7 mL), and heated for 17 h at 60 °C. At this point TLC (1:1, EtOAc/hexane) indicated the formation of a major product (R_f 0.43). The solvent was removed, and the crude material purified by flash chromatography (1:1, EtOAc/hexane) to give the inverted alcohol **26** (0.329 g, 95% yield) as a white crystalline solid. Found: C, 63.24; H, 6.75; $C_{14}H_{18}O_5$ requires: C, 63.15; H, 6.81; mp 97–98 °C; $[\alpha]_D^{26} = +34.4$ (*c*, 1.42 in $CHCl_3$); ν_{max} (NaCl) 3417 (OH) 2874–3032 (C–H), 1734 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.15 (d, 3H, H-6, *J* 6.8), 3.25 (br s, 1H, –O*H*), 3.75–3.84 (m, 4H, H-5 and CO_2*Me*), 4.65–4.69 (m, 3H, H-4 and PhC*H*$_2$), 4.96 (dd, 1H, H-3, $J_{2,3} \approx J_{3,4} \approx 5.6$), 5.08 (d, 1H, H-2, *J* 7.2), 7.27–7.36 (m, 5H, Ph); δ_C ($CDCl_3$, 100.6 MHz): 14.87 (C-6), 52.22 (CO_2CH_3), 67.10 (C-3), 72.13 (Ph*C*H$_2$), 74.01 (C-5), 81.88 (C-2), 93.45 (C-4), 127.53, 127.57, 128.36 (Ph), 138.57 (C_{IPSO}), 170.69 (C-1). MS (APCI+) *m*/*z*: 284.1 (MNH_4^+, 100%).

4.6. Methyl 2,4-anhydro-5-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-6-deoxy-L-altronate 27

TBDMS triflate (0.061 mL, 0.27 mmol) was added dropwise to a stirred solution of alcohol **26** (0.036 g, 0.135 mmol) and pyridine (0.043 mL, 0.54 mmol) in dichloromethane (0.8 mL) at −20 °C under nitrogen. The solution was stirred for a further 20 min at −20 °C, then warmed to 0 °C. After 1 h, TLC (1:2, EtOAc/hexane) indicated the formation of a major product (R_f 0.56) and the absence of any starting material (R_f 0.19). The solution was diluted with dichloromethane (10 mL), washed with water (2.5 mL), dried

over magnesium sulfate, filtered and the solvent removed. The crude product was purified by flash chromatography (1:2, EtOAc/hexane) to give fully protected altronate ester **27** (0.049 g, 95% yield) as a clear oil. Found: C, 62.65; H, 8.01; $C_{20}H_{32}O_5Si$ requires: C, 63.12; H, 8.48; HRMS *m/z* (CI+): found 398.2360 (MNH_4^+), $C_{20}H_{36}NO_5Si$ requires 398.2363; $[\alpha]_D^{22} = +1.5$ (*c*, 0.58 in $CHCl_3$); ν_{max} (NaCl) 2858–2953 (C–H), 1738, 1762 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.05, 0.06 (2 × s, 2 × 3H, Si*Me*$_2$), 0.86 (s, 9H, Si*t**Bu*), 1.15 (d, 3H, H-6, *J* 6.4), 3.75–3.81 (m, 4H, H-5 and –CO_2*Me*), 4.66 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 4.2$), 4.69 (s, 2H, PhC*H*$_2$O–), 4.95 (dd, 1H, H-3, *J* 7.0, 4.8), 5.08 (d, 1H, H-2, *J* 7.0), 7.28–7.38 (m, 5H, Ph); δ_C ($CDCl_3$, 100.6 MHz): −5.16, −5.05 (–Si(*C*H$_3$)$_2$), 15.15 (C-6), 17.72 (–Si*C*Me$_3$), 25.43 (SiC(*C*H$_3$)$_3$), 51.80 (–CO_2*C*H$_3$), 67.48 (C-3), 72.04 (Ph*C*H$_2$O–), 74.15 (C-5), 82.46 (C-2), 94.30 (C-4), 127.47, 127.56, 128.29 (Ph), 138.65 (C_{IPSO}), 170.08 (C-1). MS (ESI+) *m/z*: 381.21 (MH^+, 24%), 398.24 (MNH_4^+, 100%), 403.19 (MNa^+, 67%).

4.7. Methyl 2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-6-deoxy-L-altronate 28

A solution of benzyl ether **27** (0.343 g, 0.901 mmol) in 1,4-dioxane (5.5 mL) was stirred under hydrogen in the presence of palladium black (0.086 g). After 18 h, TLC (1:1, EtOAc/hexane) indicated the formation of one product (R_f 0.43) and the absence of any starting material (R_f 0.68). The reaction mixture was degassed, flushed with nitrogen and then filtered through Celite®. The solvent was removed to give silyl ether **28** (0.258 g, 99% yield) as a clear oil. Found: C, 53.28; H, 8.70; $C_{13}H_{26}O_5Si$ requires: C, 53.76; H, 9.02; HRMS *m/z* (CI+): found 291.1624 (MH^+), $C_{13}H_{27}O_5Si$ requires 291.1628; $[\alpha]_D^{22} = -0.3$ (*c*, 1.10 in $CHCl_3$); ν_{max} (NaCl) 3460 (O–H), 2859–2954 (C–H), 1746 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.05, 0.07 (2 × s, 2 × 3H, Si*Me*$_2$), 0.85 (s, 9H, Si*t**Bu*), 1.12 (d, 3H, H-6, *J* 6.8), 2.47 (br s, 1H, –O*H*), 3.80 (s, 3H, –CO_2*Me*), 3.99 (dq, 1H, H-5, *J* 6.8, 2.8), 4.67 (dd, 1H, H-4, *J* 5.3, 2.8), 4.94 (dd, 1H, H-3, *J* 7.1, 5.3), 5.01 (d, 1H, H-2, *J* 7.1); δ_C ($CDCl_3$, 100.6 MHz): −5.21, −4.95 (–Si(*C*H$_3$)$_2$), 16.00 (C-6), 17.72 (Si*C*Me$_3$), 25.43 (SiC(*C*H$_3$)$_3$), 51.94 (–CO_2*C*H$_3$), 65.80 (C-3), 66.33 (C-5), 82.65 (C-2), 94.65 (C-4), 169.94 (C-1). MS (TOF FI+) *m/z*: 291.15 (MH^+, 100%).

When the hydrogenation was conducted in methanol as solvents silyl ether **28** was formed in 62% yield together with methyl 2,4-anhydro-6-deoxy-L-altronate **29** (0.021 g, 31% yield) as a white crystalline solid. Found: C, 47.99; H, 7.12; $C_7H_{12}O_5$ requires: C, 47.72; H, 6.87; HRMS *m/z* (CI+): found 194.1024 (MNH_4^+), $C_7H_{13}O_5$ requires 194.1028; mp 100–101 °C; $[\alpha]_D^{22} = +48.3$ (*c*, 0.84 in H_2O); ν_{max} (KBr) 3433 (O–H), 2935 (C–H), 1737 (C=O); δ_H (D_2O, 400 MHz): 1.13 (d, 3H, H-6, *J* 7.0), 3.84 (s, 3H, –CO_2*Me*), 4.03 (dq, 1H, H-5, *J* 7.0, 4.0), 4.60 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 4.6$), 4.95 (dd, 1H, H-3, *J* 7.2, 5.6), 5.20 (d, 1H, H-2, *J* 7.2); δ_C (D_2O, 100.6 MHz): 16.25 (C-6), 53.20 (–CO_2*C*H$_3$), 66.10 (C-3), 66.92 (C-5), 82.77 (C-2), 93.56 (C-4), 172.74 (C-1). MS (APCI+) *m/z*: 177.17 (MH^+, 100%), 194.21 (MNH_4^+, 66%).

4.8. Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate 30

Triphenylphosphine (0.120 g, 0.454 mmol) in tetrahydrofuran (1.3 mL) was added dropwise to a stirred solution of silyl ether **28** (0.066 g, 0.227 mmol) in tetrahydrofuran (1.3 mL) under nitrogen at room temperature in the dark. DEAD (0.072 mL, 0.454 mmol) and DPPA (0.049 mL, 0.227 mmol) were added sequentially. After 15 h, TLC (1:2, EtOAc/hexane) revealed the formation of a major product (R_f 0.61). The solvent was removed, and the residue purified by flash chromatography (1:3, EtOAc/hexane), to give the 2,3-*cis*-D-Ala-D-Ser dipeptide scaffold **30** (0.065 g, 91% yield) as a clear oil. HRMS *m/z* (CI+): found 316.1697 (MH^+), $C_{13}H_{26}N_3O_4Si$ requires 316.1693; $[\alpha]_D^{23} = -50.9$ (*c*, 0.74 in $CHCl_3$); ν_{max} (NaCl) 2859–2954 (C–H), 2113 (N_3), 1740, 1761 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.05 (s, 6H, Si*Me*$_2$), 0.86 (s, 9H, Si*t**Bu*), 1.35 (d, 3H, H-6, *J* 6.8), 3.51 (dq, 1H, H-5, *J* 6.8, 3.7), 3.80 (s, 3H, –CO_2*Me*), 4.68 (dd, 1H, H-4, *J* 4.7, 3.7), 4.83 (dd, 1H, H-3, *J* 7.0, 4.7), 5.07 (d, 1H, H-2, *J* 7.0); δ_C ($CDCl_3$, 100.6 MHz): −5.19, −5.08 (–Si(*C*H$_3$)$_2$), 14.02 (C-6), 17.79 (–Si*C*Me$_3$), 25.43 (SiC(*C*H$_3$)$_3$), 51.91 (–CO_2*C*H$_3$), 57.55 (C-5), 68.05 (C-3), 82.19 (C-2), 93.19 (C-4), 169.60 (C-1); MS (ESI+) *m/z*: 316.2 (MH^+, 94%), 333.2 (MNH_4^+, 100%).

4.9. Methyl 2,4-anhydro-3-*O*-benzoyl-5-bromo-5,6-dideoxy-D-gulonate 31

N-Bromosuccinimide (0.595 g, 3.267 mmol) and barium carbonate (0.307 g, 1.56 mmol) were added to a solution of benzylidene acetal **12** (0.784 g, 2.97 mmol) in carbon tetrachloride (20 mL). The reaction mixture was stirred at 60 °C for 22 h, at which point TLC (1:2, EtOAc/hexane) revealed that the starting material (R_f 0.26) had been replaced by a major product (R_f 0.38). Dichloromethane (100 mL) was added to the reaction mixture, and the solution washed with brine (85 mL). The aqueous layer was further extracted with dichloromethane (3 × 50 mL), the organic fractions then combined, dried over magnesium sulfate, filtered and the solvent was removed. The crude material was purified by flash chromatography (1:3, EtOAc/hexane) to give the bromide **31** (0.875 g, 86%) as a white crystalline solid. Found: C, 48.81; H, 4.46; $C_{14}H_{15}BrO_5$ requires: C, 49.00; H, 4.41; mp 93–94 °C; $[\alpha]_D^{22} = -31.6$ (*c*, 0.97 in $CHCl_3$); ν_{max} (NaCl) 2955 (C–H), 1731 (br, 2 × C=O); δ_H ($CDCl_3$, 400 MHz): 1.72 (d, 3H, H-6, *J* 6.8), 3.86 (s, 3H, CO_2*Me*), 4.56 (dq, 1H, H-5, *J* 8.6, 6.8), 4.99 (ddd, 1H, H-4, *J* 8.6, 6.7, 0.7), 5.13 (dd, 1H, H-2, *J* 4.6, 0.7), 5.85 (dd, 1H, H-3, *J* 6.7, 4.6), 7.47–7.51 (m, 2H, *m*-Ph), 7.61–7.65 (m, 1H, *p*-Ph), 8.04–8.06 (m, 2H, *o*-Ph); δ_C ($CDCl_3$, 100.6 MHz): 21.08 (C-6), 46.65 (C-5), 52.87 (CO_2*C*H$_3$), 69.66 (C-3), 81.65 (C-2), 85.89 (C-4), 128.47, 128.87, 129.96, 134.14 (Ph), 165.09, 169.46 (2 × C=O).

4.10. Methyl 2,4-anhydro-5-azido-3-*O*-benzoyl-5-deoxy-L-rhamnonate 32

Sodium azide (1.25 g, 19.2 mmol) was added to a solution of the D-gulonate bromide **31** (4.40 g, 12.8 mmol)

in DMSO (30 mL) under nitrogen. The reaction mixture was heated at 85 °C for 17 h at which point it was diluted with dichloromethane (150 mL). TLC (1:2, EtOAc/hexane) revealed that both the starting material and product had R_f 0.46. The solution was washed with water (30 mL), and the aqueous layer further extracted with dichloromethane (2 × 150 mL); the organic fractions were then combined, dried over magnesium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography (1:2, EtOAc/hexane) to give azide **32** (2.38 g, 61%) as a colourless oil. Found: C, 55.30; H, 4.95; N, 13.37; $C_{14}H_{15}N_3O_5$ requires: C, 55.08; H, 4.95; N, 13.76; $[\alpha]_D^{22} = +43.5$ (*c*, 0.99 in $CHCl_3$); ν_{max} (NaCl) 2954 (C–H), 2108 (N_3), 1720 (br, 2 × C=O); δ_H ($CDCl_3$, 400 MHz): 1.38 (d, 3H, H-6, *J* 6.5), 3.87 (s, 3H, CO_2Me), 4.10 (dq, 1H, H-5, *J* 8.4, 6.5), 4.75 (dd, 1H, H-4, *J* 8.4, 6.5), 5.12 (d, 1H, H-2, *J* 4.6), 5.90 (dd, 1H, H-3, *J* 6.5, 4.6), 7.47–7.51 (m, 2H, *m*-Ph), 7.60–7.65 (m, 1H, *p*-Ph), 8.08–8.10 (m, 2H, *o*-Ph); δ_C ($CDCl_3$, 100.6 MHz): 14.75 (C-6), 52.92 (CO_2CH_3), 55.92 (C-5), 69.28 (C-3), 82.32 (C-2), 84.66 (C-4), 128.75–133.99 (Ph), 165.12, 169.64 (2 × C=O).

4.11. Methyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate 11

1 M Aqueous sodium hydroxide (31.2 mL, 31.2 mmol) was added dropwise to a solution of azide **32** (2.38 g, 7.80 mmol) in tetrahydrofuran (55 mL) and water (7.7 mL) under nitrogen. The solution was stirred at room temperature overnight, after which TLC (CMAH, 60:30:3:5) indicated the formation of one UV-inactive product (R_f 0.34). Methanol (1550 mL) and concd aqueous hydrochloric acid (15.5 mL) were then added to the solution. After a further 24 h, TLC (1:2, EtOAc/hexane) indicated the formation of one product (R_f 0.17). The solution was neutralised with $NaHCO_3$ to pH 6, filtered and half the solvent removed. Water (250 mL) was added and the solution washed with dichloromethane (3 × 500 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed to give azide **11** (1.40 g, 89%) as a white crystalline solid. Found: C, 42.13; H, 5.77; N, 20.90; $C_7H_{11}N_3O_4$ requires: C, 41.79; H, 5.51; N, 20.89; mp 55–56 °C; $[\alpha]_D^{22} = +75.1$ (*c*, 0.97 in $CHCl_3$); ν_{max} (NaCl) 3433 (O–H), 2939 (C–H), 2099 (N_3), 1746 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.32 (d, 3H, H-6, *J* 6.8), 3.54 (d, 1H, –OH, *J* 8.4), 3.81 (s, 3H, CO_2Me), 4.10 (dq, 1H, H-5, *J* 6.8, 6.6), 4.56 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 6.6$), 4.85 (m, 1H, H-3), 4.99 (d, 1H, H-2, *J* 5.2); δ_C ($CDCl_3$, 100.6 MHz): 15.06 (C-6), 52.60 ($-CO_2CH_3$), 58.02 (C-5), 70.26 (C-3), 85.67 (C-2), 86.21 (C-4), 170.77 (C-1); MS (CI+) *m/z*: 219.1 (MNH_4^+, 100%), 202.1 (MH^+, 11%).

4.12. Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate 35

TBDMS triflate (0.747 mL, 3.26 mmol) was added dropwise to a stirred solution of azido alcohol **11** (0.328 g, 1.63 mmol) and pyridine (0.525 mL, 6.52 mmol) in dichloromethane (6.5 mL) at −20 °C under nitrogen. The solution was stirred for a further 20 min at −20 °C and then warmed to 0 °C. After 2 h, TLC (1:2, EtOAc/hexane) indicated the formation of one product (R_f 0.62) and the absence of the starting material (R_f 0.28). The solution was diluted in dichloromethane (65 mL), washed with water (16 mL), dried over magnesium sulfate, filtered and the solvent removed. The residue was purified by flash chromatography (2:3, EtOAc/hexane), to give L-ala-D-ser scaffold **35** (0.445 g, 87%) as a clear oil. HRMS *m/z* (CI+): found 333.1954 (MNH_4^+); $C_{13}H_{29}N_4O_4Si$ requires 333.1958; $[\alpha]_D^{22}$=+44.8 (*c*, 1.16 in $CHCl_3$); ν_{max} (NaCl) 2936 (C–H), 2096 (N_3), 1755 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.11 (s, 6H, $SiMe_2$), 0.92 (s, 9H, Si^tBu), 1.35 (d, 3H, H-6, *J* 6.5), 3.81 (s, 3H, $-CO_2Me$), 4.06 (dq, 1H, H-5, *J* 8.6, 6.5), 4.45 (dd, 1H, H-4, *J* 8.6, 6.0), 4.78 (dd, 1H, H-3, *J* 6.0, 4.7), 4.82 (d, 1H, H-2, *J* 4.7); δ_C ($CDCl_3$, 100.6 MHz): −5.25, −5.11 ($-Si(CH_3)_2$), 14.55 (C-6), 17.94 ($-SiCMe_3$), 25.56 ($SiC(CH_3)_3$), 52.21 ($-CO_2CH_3$), 54.97 (C-5), 69.68 (C-3), 85.69 (C-2), 86.52 (C-4), 170.64 (C-1); MS (APCI+) *m/z*: 200.16 (100%), 316.20 (MH^+, 23%), 333.22 (MNH_4^+, 83%).

4.13. Methyl 2,4-anhydro-5-azido-5-deoxy-3-*O*-trifluoromethanesulfonyl-L-rhamnonate 34

Triflic anhydride (1.41 mL, 8.2 mmol) was added dropwise to a solution of pyridine (1.68 mL, 20.5 mmol) and alcohol **11** (0.82 g, 4.1 mmol) in dichloromethane (16 mL) under nitrogen at −78 °C. The reaction mixture was stirred at −78 °C for a further 20 min, before warming to 0 °C. After 2.25 h, TLC (1:1, EtOAc/hexane) revealed that the starting material (R_f 0.59) had been completely replaced by one product (R_f 0.69). At this point, the reaction mixture was diluted with dichloromethane (160 mL), washed with 0.1 M aqueous hydrochloric acid (80 mL) and then water (80 mL). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography (2:5, EtOAc/hexane) to give triflate **34** (1.36 g, 100%) as a clear oil. Found: C, 29.21; H, 3.10; N, 12.23; $C_8H_{10}F_3N_3O_6S$ requires: C, 28.83; H, 3.02; N, 12.61; $[\alpha]_D^{25} = +8.6$ (*c*, 0.92 in $CHCl_3$); ν_{max} (NaCl) 2961 (C–H), 2113 (N_3), 1761 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.41 (d, 3H, H-6, *J* 6.6), 3.87 (s, 3H, $-CO_2Me$), 4.06 (dq, 1H, H-5, *J* 9.2, 6.6), 4.62 (ddd, 1H, H-4, *J* 9.2, 5.9, 1.2), 5.15 (dd, 1H, H-2, *J* 4.8, 1.2), 5.68 (dd, 1H, H-3, *J* 5.9, 4.8); δ_C ($CDCl_3$, 100.6 MHz): 14.34 (C-6), 53.09 ($-CO_2CH_3$), 55.18 (C-5), 78.65 (C-3), 81.14 (C-2), 83.76 (C-4), 113.52, 116.70, 119.88, 123.06 (–OTf), 167.76 (C-1); MS (APCI+) *m/z*: 351.00 (MNH_4^+, 100%).

4.14. Methyl 2,4-anhydro-5-azido-5,6-di-deoxy-L-altronate 15

Caesium trifluoroacetate (0.214 g, 0.87 mmol) was added to a solution of triflate **34** (0.097 g, 0.29 mmol) in butanone (1.5 mL), and heated for 3.5 h at 60 °C. At this point, TLC (1:1, EtOAc/hexane) indicated that the starting material (R_f 0.59) had been replaced by a major product (R_f 0.29). The solvent was removed, and the crude material purified by flash chromatography (1:1, EtOAc/hexane) to give azido ester **15** (0.058 g, 99%) as a white crystalline solid. Found: C, 41.66; H, 5.52; N, 20.82; $C_7H_{11}N_3O_4$ requires: C, 41.79; H, 5.51; N,

20.89; mp 78–80 °C; $[\alpha]_D^{26} = +15.7$ (*c*, 0.99 in $CHCl_3$); ν_{max} (NaCl) 3445 (O–H), 2921–2976 (C–H), 2094, 2136 (N_3), 1740 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.20 (d, 3H, H-6, *J* 6.8), 3.25 (br s, 1H, –OH), 3.80–3.85 (m, 4H, $–CO_2Me$ and H-5), 4.68 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 4.8$), 4.90 (dd, 1H, H-3, $J_{2,3} \approx J_{3,4} \approx 5.8$), 5.11 (d, 1H, H-2, *J* 7.2); δ_C ($CDCl_3$, 100.6 MHz): 14.10 (C-6), 52.41 ($–CO_2CH_3$), 58.37 (C-5), 67.21 (C-3), 81.85 (C-2), 92.34 (C-4), 170.33 (C-1); MS (APCI+) *m/z*: 202.1 (MH^+, 43%), 219.1 (MNH_4^+, 100%).

4.15. Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-di-deoxy-L-altronate 33

TBDMS triflate (1.32 mL, 5.78 mmol) was added dropwise to a solution of alcohol **15** (0.582 g, 2.89 mmol) and pyridine (0.93 mL, 11.56 mmol) in dichloromethane (11 mL) at −20 °C under nitrogen. The reaction mixture was stirred for a further 20 min at −20 °C, and then warmed to 0 °C. After 1.5 h, TLC (1:2, EtOAc/hexane) indicated the formation of a major product (R_f 0.52) and the absence of starting material (R_f 0.10). The solution was diluted in dichloromethane (150 mL), washed with water (40 mL), dried over magnesium sulfate, filtered and the solvent removed. The residue was purified by flash chromatography (1:2, EtOAc/hexane) to give the silyl protected 2,3-*cis*-L-Ala-D-Ser dipeptide scaffold **33** (0.906 g, 99%) as a clear oil. Found: C, 49.71; H, 8.04; N, 13.05; $C_{13}H_{25}N_3O_4Si$ requires: C, 49.50; H, 7.99; N, 13.32; $[\alpha]_D^{25} = -7.1$ (*c*, 0.94 in $CHCl_3$); ν_{max} (NaCl) 2859–2954 (C–H), 2128 (N_3), 1740, 1762 (C=O); δ_H ($CDCl_3$, 400 MHz): 0.06, 0.08 (2 × s, 2 × 3H, $SiMe_2$), 0.86 (s, 9H, Si^tBu), 1.20 (d, 3H, H-6, *J* 6.8), 3.76 (dq, 1H, H-5, *J* 5.2, 6.8), 3.80 (s, 3H, $–CO_2Me$), 4.65 (ddd, 1H, H-4, *J* 0.8, $J_{3,4} \approx J_{4,5} \approx 5.0$), 4.82 (dd, 1H, H-3, *J* 7.2, 4.8), 5.07 (dd, 1H, H-2, *J* 7.2, 0.8); δ_C ($CDCl_3$, 100.6 MHz): −5.26, −5.03 ($–Si(CH_3)_2$), 14.51 (C-6), 17.76 ($–SiCMe_3$), 25.41 ($SiC(CH_3)_3$), 51.94 ($–CO_2CH_3$), 58.57 (C-5), 67.83 (C-3), 82.46 (C-2), 93.12 (C-4), 169.62 (C-1); MS (APCI+) *m/z*: 258.1 (100%), 316.2 (MH^+, 93%), 333.2 (MNH_4^+, 95%).

4.16. Methyl 2,4-anhydro-5-azido-3-*O*-benzoyl-5-deoxy-D-lyxonate 37

Sodium azide (449 mg, 6.90 mmol) was added in one portion to a solution of bromide **36** (1.033 g, 3.14 mmol) in DMF (29 mL). The reaction mixture was stirred at 70 °C overnight after which complete conversion of the starting material to one major product was seen (R_f 0.55, 1:2, EtOAc/hexane). A few drops of water were added and the solvent removed in vacuo. The resulting solid was dissolved in ethyl acetate (150 mL) and washed with brine (100 mL). The aqueous layer was further extracted with ethyl acetate (3 × 70 mL), dried (magnesium sulfate) and the solvent was removed. The residue was purified by column chromatography (1:6, EtOAc/hexane) to give the azide **37** (820 mg, 89% yield) as a colourless oil. HRMS *m/z* (CI+): found 292.0936 ($M+H^+$); $C_{13}H_{14}N_3O_5$ requires 292.0933; $[\alpha]_D^{22} = +103.5$ (*c*, 1.03 in $CHCl_3$); ν_{max} (thin film): 2105 (N_3), 1728 (br, C=O); δ_H ($CDCl_3$, 400 MHz): 3.67 (1H, dd, H-5, *J* 13.5, 5.0), 3.72 (1H, dd, H-5′ *J* 13.5, 6.0), 3.88 (3H, s, OMe), 5.15 (1H, ddt, H-4, *J* 5.9, 5.2, 0.7), 5.27 (1H, dd, H-2, *J* 5.1, 0.7), 5.82 (1H, dd, H-3, *J* 6.6, 5.2), 7.48 (2H, m, *m*-ArH), 7.64 (1H, m, *p*-ArH), 8.18 (2H, m, *o*-ArH); δ_C ($CDCl_3$, 100.6 MHz): 50.5 (C-5), 69.7 (C-3), 82.1 (C-4, C-2), 128.3 (*m*-ArCH), 128.7 (*o*-ArCH), 129.9 (*p*-ArCH), 134.0 (ArC), 165.2 (Ph**C**=O), 169.4 (C=O); *m/z* (APCI+ve): 292 ($M+H^+$, 12%), 105 (100%).

4.17. Methyl 5-azido-4-formyl-3-oxa-pentanoate 38

Sodium methoxide (1.9 mg, 0.035 mmol) in methanol (0.036 mL) was added to a solution of azide **37** (21 mg, 0.07 mmol) in methanol (0.57 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h after which time a further portion of sodium methoxide (1 mg, 0.018 mmol) in methanol (0.018 mL) was added. After another hour, very little starting material (R_f 0.61) was seen to remain by TLC (1:2 EtOAc/hexane) and the formation of three products observed (R_f 0.89, 0.27 and 0.15). The mixture was neutralised with Amberlite resin (IR 120, H^+ form), filtered and concentrated under reduced pressure. The crude mixture was partially purified by column chromatography (1:5 EtOAc/hexane). The spectral data of the major product was consistent with structure **38** (R_f 0.27) (5 mg, 37%). ν_{max} (thin film): 2105 (s, N_3), 1760 (s, C=O), 1704 (s, C=O), 1620 (s); δ_H ($CDCl_3$, 200 MHz): 3.79 (1H, s, H-4), 3.82 (3H, s, OMe), 4.55 (2H, s, H-5), 5.15–5.25 (2H, dd, H-2, *J* 3.7, 16.5), 9.35 (1H, s, CHO).

4.18. Methyl 2,4-anhydro-5-azido-5-deoxy-D-lyxonate 41

Aqueous sodium hydroxide (1 M, 9 mL) was added to a solution of azide **37** (655 mg, 2.2 mmol) in a mixture of THF (14 mL) and water (2 mL). After 12 h, all starting material had been converted to one spot by TLC (R_f 0.53, chloroform/methanol/water/acetic acid, 60:30:5:3). A 1% solution of concentrated hydrochloric acid (3 mL) in methanol (300 mL) was added to sodium salt **42** and the reaction stirred at room temperature overnight to give one major product (R_f 0.32, 1:2 EtOAc/hexane). The reaction mixture was neutralised with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. The residue was purified by column chromatography to give the deprotected azide **41** as a white crystalline solid (377 mg, 90%). Found: C, 38.59; H, 4.81; N, 22.59; $C_6H_9N_3O_4$ requires: C, 38.51; H, 4.85; N, 22.45; mp 64–67 °C; $[\alpha]_D^{22} = +8.8$ (*c*, 0.98 in $CHCl_3$); ν_{max} (thin film): 3440 (br, OH), 2106 (N_3), 1739 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.62 (2H, dd, H-5, H-5′, *J* 13.6, 3.9), 3.82 (3H, s, OMe), 3.79–3.85 (1H, br m, OH), 4.87 (1H, dd, H-3, *J* 6.8, 5.3), 4.91–4.95 (1H, m, H-4), 5.77 (1H, d, H-2, *J* 5.3); δ_C ($CDCl_3$, 100.6 MHz): 51.5 (C-5), 52.9 (OCH_3), 70.5 (C-3), 84.1 (C-4), 86.8 (C-2), 171.0 (C=O); *m/z* (APCI+ve): 205 ($M + NH_4^+$, 75%), 188 ($M+H^+$, 22%), 162 (100%), 160 ($M+H^+-N_2$, 52%).

4.19. Isopropyl 2,4-anhydro-5-azido-5-deoxy-D-lyxonate 40

A solution of methyl ester **41** (225 mg, 1.2 mmol) in isopropanol (2 mL) was heated with *para*-toluenesulfonic

acid (*p*-TSA) (4.6 mg, 0.024 mmol) at 70 °C overnight, after which TLC showed that all the starting material had been converted to one major product (R_f 0.79, 1:1 EtOAc/hexane). Solid sodium bicarbonate was added to neutralise the solution to pH 5. The resulting mixture was pre-absorbed onto silica gel and purified by column chromatography (1:5, EtOAc/hexane) to yield isopropyl azidoester **40** as a white crystalline solid (256 mg, 88%). Found: C, 44.53; H, 5.96; N, 19.10; $C_8H_{13}N_3O_4$ requires: C, 44.65; H, 6.09; N, 19.53; HRMS: *m/z* (CI+) found 233.1245 ($M + NH_4^+$); $C_8H_{17}N_4O_4$ requires 233.1249; mp 57–59 °C; $[\alpha]_D^{23} = +26.4$ (*c*, 0.95 in $CHCl_3$); ν_{max} (thin film): 3368 (m, br, OH), 2111 (s, N_3), 1738 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.29 (3H, d, (C*H*$_3$)C, *J* 6.3), 1.31 (3H, d, (C*H*$_3$)′C, *J* 6.3), 3.42–3.58 (1H, br, OH), 3.60 (1H, dd, H-5, *J* 13.6, 3.6), 3.84 (1H, dd, H-5′, *J* 13.6, 4.6), 4.83 (1H, dd, H-3, *J* 6.8, 5.3), 4.91–4.95 (1H, m, H-4), 5.02 (1H, dd, H-2, *J* 5.3, 0.8), 5.09–5.19 (1H, septet, C*H*$(CH_3)_2$, *J* 6.3); δ_C ($CDCl_3$, 100.6 MHz): 21.7 (2C, C(*C*H$_3$)$_2$), 51.2 (C-5), 69.4 (C-3), 70.1 (C-4), 83.4 (*C*$(CH_3)_2$), 86.6 (C-2), 169.6 (C=O); *m/z* (APCI+ve): 233 ($M + NH_4^+$, 62%), 216 ($M+H^+$, 5%), 190 (100%).

4.20. Isopropyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate 45

TBDMS triflate (1.17 mL, 5.08 mmol) was added dropwise to a solution of azide **40** (546 mg, 2.54 mmol) in dichloromethane (15 mL) and pyridine (0.82 mL, 10.16 mmol). The reaction mixture was stirred for 20 min at −20 °C. The solution was allowed to warm to 0 °C and after 1.25 h, TLC (1:2, EtOAc/hexane) showed the complete conversion to one product (R_f 1.0). The reaction was diluted with dichloromethane (40 mL), washed with water (10 mL), dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by column chromatography (1:2, EtOAc/hexane) to give title compound **45** as a colourless oil (822 mg, 98%). Found: C, 51.26; H, 8.25; N, 12.43; $C_{14}H_{27}N_3O_4Si$ requires: C, 51.04; H, 8.26; N, 12.75; $[\alpha]_D^{24} = -8.8$ (*c*, 0.98 in $CHCl_3$); ν_{max} (thin film): 2102 (s, N_3), 1751 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 0.08 (3H, s, SiC*H*$_3$), 0.11 (3H, s, SiC*H*$_3$), 0.91 (9H, s, SiC(C*H*$_3$), 1.30 (3H, s, OCH(C*H*$_3$)), 1.29 (3H, s, OCH(C*H*$_3$)), 3.60 (1H, dd, H5, *J* 13.1, 5.4), 3.71 (1H, dd, H-5′, *J* 13.1, 6.5), 4.78 (1H, m, H-3), 4.86 (1H, m, H-4), 4.89 (1H, d, H-2, *J* 4.9), 5.14 (1H, septet, C*H*$(CH_3)_2$, *J* 6.2); δ_C ($CDCl_3$, 100 MHz): −2.5, −2.1 (2 × SiC*H*$_3$), 20.8 (Si*C*$(CH_3)_3$), 24.6 (OCH(*C*H$_3$)$_2$), 28.5 (SiC(*C*H$_3$)$_3$), 53.3 (C-5), 72.0 (O*C*H$(CH_3)_2$), 72.2 (C-3), 86.5 (C-4), 88.9 (C-2), 172.4 (C=O); *m/z* (APCI+ve): 302 ($M+H^+-N_2$, 20%), 128 (100%).

4.21. Isopropyl 2,4-anhydro-5-azido-5-deoxy-3-*O*-trifluoromethanesulfonyl-D-lyxonate 39

Triflic anhydride (0.125 mL, 0.74 mmol) was added dropwise to a solution of alcohol **40** (100 mg, 0.465 mmol) in dichloromethane (8 mL) and pyridine (0.113 mL, 0.4 mmol) at −30 °C. The reaction mixture was stirred at −30 to −10 °C for 2.5 h when TLC (1:3, EtOAc/hexane) showed the complete conversion of starting material (R_f 0.17) to one product (R_f 0.72). The solution was diluted with dichloromethane (40 mL) and washed with 2 M aqueous hydrochloric acid (20 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers washed with brine (30 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (1:3, EtOAc/hexane) to yield triflate **39** as a colourless oil (155 mg, 96%). Found: C, 31.58; H, 3.67; N, 12.04; $C_9H_{12}F_3N_3O_6S$ requires: C, 31.13; H, 3.48; N, 12.10; $[\alpha]_D^{26} = +41.8$ (*c*, 1.04 in $CHCl_3$); ν_{max} (thin film): 2111 (s, N_3), 1750 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.31 (3H, d, OCH(C*H*$_3$)$_2$, *J* 6.3), 1.32 (3H, d, OCH(C*H*$_3$)$_2$, *J* 6.3), 3.72 (1H, dd, H-5, *J* 13.5, 5.5), 3.77 (1H, dd, H-5, *J* 13.5, 5.5), 5.04 (1H, a-dq, H-4, *J* 5.6, 1.1), 5.16 (1H, septet, C*H*$(CH_3)_2$, *J* 6.3), 5.23 (1H, dd, H-2, *J* 5.1, 1.3), 5.68 (1H, a-t, H-3, *J* 5.8); δ_C ($CDCl_3$, 100 MHz): 21.5, (2 × OCH(*C*H$_3$)$_2$), 50.0 (C-5), 70.6 (O*C*H$(CH_3)_2$), 78.1 (C-3), 81.0 (C-4), 81.5 (C-2), 116.7, 119.9 (CF_3), 166.7 (C=O); *m/z* (APCI+ve): 365 ($M + NH_4^+$, 100%).

4.22. Isopropyl 2,4-anhydro-5-azido-5-deoxy-D-arabinonate 43

Caesium trifluoroacetate (366 mg, 1.49 mmol) was added to a solution of triflate **39** (129 mg, 0.37 mmol) in 2-butanone (4 mL). The reaction mixture was heated to 60 °C for 18 h after which TLC (1:3, EtOAc/hexane) showed conversion of the starting material (R_f 0.72) to one product (R_f 0.07). The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (1:1, EtOAc/hexane) to give alcohol **43** as a white solid (78 mg, 98%). Found: C, 44.9; H, 6.11; N, 19.52; $C_8H_{13}N_3O_4$ requires: C, 44.65; H, 6.09; N, 19.53; mp 91–93 °C (from EtOAc/hexane); $[\alpha]_D^{26} = +45.9$ (*c*, 1.04 in $CHCl_3$); ν_{max} (thin film): 3412 (br m, OH), 2109 (m, N_3), 1726 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.31 (3H, d, CH(C*H*$_3$)$_2$, *J* 6.2), 1.33 (3H, d, CH(C*H*$_3$)$_2$, *J* 6.2), 2.80–3.00 (1H, br, OH), 3.38–3.43 (1H, dd, H-5, *J* 14.0, 3.0), 3.63–3.68 (1H, dd, H-5′, *J* 14.0, 2.9), 4.90–5.0 (2H, m, H-3, H-4), 5.07 (1H, d, H-2, *J* 6.1), 5.2 (1H, septet, *J* 6.3); δ_C ($CDCl_3$, 100 MHz): 21.8 (CH(*C*H$_3$)$_2$), 21.9 (CH(*C*H$_3$)$_2$), 52.4 (C-5), 67.6 (C-3), 69.6 (*C*H$(CH_3)_2$), 81.7 (C-2), 89.0 (C4), 169.4 (C=O); *m/z* (APCI+ve): 233 ($M + NH_4^+$, 100%), 216 ($M+H^+$, 35%).

4.23. Isopropyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-arabinonate 44

TBDMS triflate (0.17 mL, 0.72 mmol) was added to a solution of alcohol **43** (78 mg, 0.36 mmol) in dichloromethane (2.2 mL) and pyridine (0.12 mL, 1.45 mmol) added at −20 °C. The reaction mixture was stirred at −20 °C for 20 min and then allowed to warm to 0 °C. After 1 h at 0 °C, TLC (1:2, EtOAc/hexane) showed complete conversion of starting material (R_f 0.21) to one product (R_f 0.86). The reaction was diluted with dichloromethane (30 mL), washed with water (10 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column

chromatography (1:2, EtOAc/hexane) to give azide **44** as a colourless oil (57 mg, 48%). Found: C, 51.09; H, 8.71; N, 12.36; $C_{14}H_{27}N_3O_4Si$ requires: C, 51.04; H, 8.26; N, 12.75; $[\alpha]_D^{26} = +50.3$ (*c*, 0.815 in $CHCl_3$); ν_{max} (thin film): 2105 (s, N_3), 1753, 1732 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 0.051 (3H, s, $SiCH_3$), 0.054 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.30 (3H, d, $CH(CH_3)_2$, *J* 6.3), 1.31 (3H, d, $CH(CH_3)_2$, *J* 6.3), 3.31–3.35 (1H, dd, H-5, *J* 14.0, 3.1), 3.60–3.65 (1H, dd, H-5′, *J* 14.0, 3.1), 4.86–4.93 (2H, m, H-3, H-4), 5.02 (1H, d, H-2, *J* 6.8), 5.09–5.18 (1H, septet, $CH(CH_3)_2$, *J* 6.3); δ_C ($CDCl_3$, 100 MHz): −5.2 ($SiCH_3$), −5.0 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 21.9 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 25.6 (×2) ($SiC(CH_3)_3$), 52.3 (C-5), 67.7 (C-3), 69.0 ($CH(CH_3)_2$), 82.6 (C-2), 89.8 (C-4), 168.7 (C=O); *m/z* (APCI+ve): 347 ($M + NH_4^+$, 99%), 330 ($M+H^+$, 100%).

Acknowledgements

Support from EPSRC studentships [to S.W.J. and S.F.J.] are gratefully acknowledged.

References

1. Edwards, A. A.; Ichihara, O.; Murfin, S.; Wilkes, R.; Watkin, D. J.; Fleet, G. W. J. *J. Comb. Chem.* **2004**, *6*, 230–238.
2. Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253; Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421–435; Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; Mayes, B. A.; Simon, L.; Watkin, D. J.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 157–162; Chakraborty, T. K.; Srinivasi, P.; Tapadar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *116*, 187–207.
3. Gregar, T. Q.; Gervay-Hague, J. *J. Org. Chem.* **2004**, *69*, 1001–1009; Kriek, N. M. A. J.; van der Hout, E.; Kelly, P.; van Meijgaarden, K. E.; Geluk, A.; Ottenhoff, T. H. M.; van der Marel, G. A.; Overhand, M.; van Boom, J. H.; Valentijn, A. R. P. M.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2003**, 2418–2427; El Oualid, F.; Bruining, L.; Leroy, I. M.; Cohen, L. H.; van Boom, J. H.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Helv. Chim. Acta* **2002**, *85*, 3455–3472; Aguilera, B.; Siegal, G.; Overkleeft, H. S.; Meeuwenoord, N. J.; Rutjes, F. P. J. T.; van Hest, J. C. M.; Schoemaker, H. E.; van der Marel, G. A.; van Boom, J. H.; Overhand, M. *Eur. J. Org. Chem.* **2001**, 1541–1547; Overkleeft, H. S.; Verhelst, S. H. L.; Pieterman, E.; Meeuwenoord, W. J.; Overhand, M.; Cohen, L. H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1999**, *40*, 4103–4106.
4. Chung, Y.-K.; Claridge, T. D. W.; Fleet, G. W. J.; Johnson, S. W.; Jones, J. H.; Lumbard, K. W.; Stachulski, A. V. *J. Peptide Sci.* **2004**, *10*, 1–7.
5. Grotenbreg, G. M.; Timmer, M. S. M.; Llamas-Saiz, A. L.; Verdoes, M.; van der Marel, G. A.; van Raaij, M. J.; Overkleeft, H. S.; Overhand, M. *J. Am. Chem. Soc.* **2004**, *126*, 3444–3446; van Well, R. M.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; van Boom, J. H.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822–10829; 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; Chakraborty, T. K.; Srinivasu, P.; Madhavendra, S. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3573–3577; Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Madhavendra, S. S.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 2853–2859; Chakraborty, T. K.; Jayaprakash, S.; Diwan, P. V.; Nagaraj, R.; Jampani, S. R. B.; Kunwar, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 12962–12963.
6. Johnson, S. W.; Angus, D.; Taillefumier, C.; Jones, J. H.; Watkin, D. J.; Floyd, E.; Buchanan, J. G.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 4113–4125.
7. Johnson, S. W.; Jenkinson (née Barker), S. F.; Angus, D.; Taillefumier, C.; Jones, J. H.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, in press.
8. Claridge, T. D. W.; Goodman, J. M.; Moreno, A.; Angus, D.; Barker, S. F.; Taillefumier, C.; Watterson, M. P.; Fleet, G. W. J. *Tetrahedron Lett.* **2001**, *42*, 4251–4254.
9. Jenkinson (née Barker), S. F.; Harris, T.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, in press.
10. Barker, S. F.; Angus, D.; Taillefumier, C.; Probert, M. R.; Watkin, D. J.; Watterson, M. P.; Claridge, T. D. W.; Hungerford, N. L.; Fleet, G. W. J. *Tetrahedron Lett.* **2001**, *42*, 4247–4250.
11. Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041–2042; Smith, M. D.; Claridge, T. D. W.; Sansom, M. S. P.; Fleet, G. W. J. *Org. Biomol. Chem.* **2003**, *1*, 3647–3655; Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666–3679.
12. 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*, 2199–2202.
13. DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*(5), 669–672.
14. (a) Failla, D. L.; Hullar, T. L.; Sisken, S. B. *Chem. Commun.* **1966**, *20*, 716–717; (b) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86–88; (c) Hanessian, S. *Adv. Chem. Ser.* **1968**, *74*, 159; (d) Hullar, T. L.; Siskin, S. B. *J. Org. Chem.* **1970**, *35*, 225–228;.
15. Watkin, D. J.; Johnson, S. W.; Jones, J. H.; Fleet, G. W. J. *Acta Cryst.*, in preparation.
16. Johnson, S. W.; Jenkinson (nee Barker), S. F.; Angus, D.; Perez-Victoria, I.; Claridge, T. D. W.; Fleet, G. W. J.; Jones, J. H. *J. Peptide Sci.*, in preparation.