Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 15 (2004) 2667–2679

Tetrahedron: *Asymmetry*

Oxetane *cis*- and *trans* β-amino-acid scaffolds from D-xylose by efficient S_N2 reactions in oxetane rings: methyl and hydroxymethyl analogues of the antibiotic oxetin, an oxetane β-amino-acid

Sarah F. Jenkinson (née Barker), Timothy Harris and George W. J. Fleet*

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

Received 23 June 2004; accepted 14 July 2004

Abstract—Highly regioselective reactions of a benzylidene-protected oxetane with (i) triethylsilane-trifluoroacetic acid and (ii) Hanessian–Hullar bromination provide efficient access to 3-hydroxyoxetane carboxylates in which only the C-3 OH is unprotected. Subsequent nucleophilic displacements of the corresponding triflates by azide proceeds in consistently excellent yields without any elimination to provide syntheses of scaffolds for a range of methyl and hydroxymethyl analogues of the antibiotic oxetin, a naturally occurring oxetane *cis*-β-amino acid.

---

1. Introduction

Oxetin **1** is a naturally occurring antibiotic[1] with the unique structure of a *cis*-β-amino acid containing an oxetane ring; relatively little synthetic work has been reported on this compound[2] and there are no reports of the incorporation of oxetin into oligopeptides. No mechanism of action has been proposed for oxetin. Recently a structurally related material, bradyoxetin, has been defined as the chemical signal responsible for gene regulation in *Bradyrhizobium japonicum*, a symbiotic bacterium that nodulates soybean;[3] small molecules which control signalling pathways in bacteria may provide new mechanisms for antibiotic chemotherapy.[4]

Herein we report the synthesis of protected hydroxymethyl oxetin analogues of the *trans*-**2** and **3** and of the *cis*-**4** and **5**-β-azido-oxetane-2-carboxylates, and of the methyl analogue **6** from D-xylose **7**.

2. Results and discussion

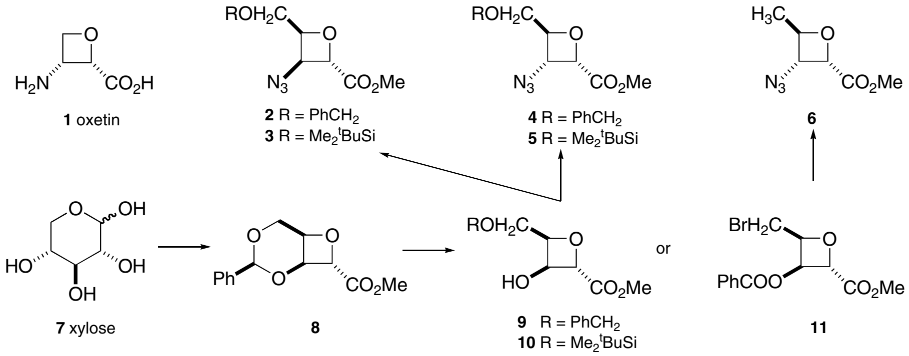
The key steps (Scheme 1) are (i) the formation from a suitably protected xylose derivative of the benzylidene-protected oxetane ring **8**, (ii) the highly regioselective ring openings of the acetal in **8** to give the benzyl either **9** or the bromomethyl derivative **11**, and (iii) the subsequent nucleophilic displacements of the C-3 OH to introduce the azido function. Some of this work has already been reported in a preliminary form.[5,6]

As well as the synthesis of oxetin analogues, the azido-ester oxetanes provide β-amino acid scaffolds for the study of secondary structures in foldamers in homooligomers. Gellman et al.[7,8] and Seebach et al.[9] have pioneered and developed the idea that relatively small molecules containing β-amino acid residues will have restricted conformations; this predisposition may be summarised as the consistent adoption of various helical motifs.[10] Extensive efforts have been made to validate structural studies by circular dichroism[11] and other techniques. Subsequent theoretical studies are in agreement with the experimental results that β-peptides have a surprising reduction in the dimensionality of freedom of motion.[12] A number of biological properties have arisen from this work allowing the generation of novel synthetic antibiotic[13] and nonhaemolytic β-amino-acid oligomers,[14] the study of the interactions of antimicrobial 14-helical β-peptides with membranes[15] and of the selective binding of TAR RNA by a Tat-derived β-peptide,[16] the inhibition of fat and cholesterol absorption,[17] β-peptide mimics of somatostatin,[18] and

---

* 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.2004.07.031



Scheme 1.

the generation of anti-proliferatives against human cancer cell growth.[19]

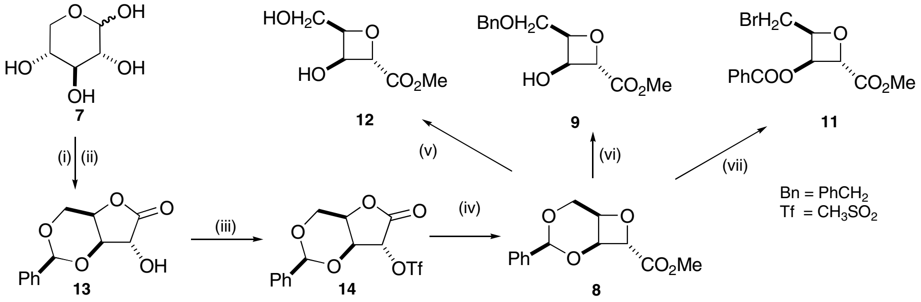
Currently there is considerable interest in the preparation of new β-amino acids as evidenced by synthetic efforts reported during the first three months of 2004;[20] these include procedures involving asymmetric synthesis.[21] While *trans*-cyclopentane amino acids were the key alicyclic template for Gellman's design of the helical structure in β-peptides, the synthesis of cyclopentane *cis*-β-amino acids as analogues of *cis*-pentacin[22] have also been investigated. A bicyclic *cis*-pentacin derivative was designed as a novel reverse turn inducer in a GnRH mimetic.[23] Cyclobutane[24] and cyclopropane[25] β-amino acids have also been used as foldameric scaffolds.

Sugar amino acids (SAA) provide a wide range of peptidomimetic scaffolds not only with the propensity to induce secondary structures but also with the potential of adjusting the solubility of oligopeptides[26] and of analogues[27] with a greater stability to peptide cleavage. As a consequence, SAA have been used as candidates in the synthesis of combinatorial libraries.[28] However, there have been very few reports of the synthesis of β-SAA.[29] Linear oligomers of conformationally locked[30,31] SAA, including those which possess tetrahydropyran[32] and tetrahydrofuran[33] rings, provide examples of relatively small molecules predisposed towards formation of secondary structures.[34,35] Examples include repeating β-turn[36] and 16-helix[37] structures from diastereomers of a δ-amino acid template. Oxetane rings may be conformationally less flexible and provide a new class of foldamers with access to a range of novel secondary structures.

2.1. Synthesis and reactions of the benzylidene-protected oxetane carboxylate

Oxetanes can be readily prepared in good yield by treatment of α-triflates of γ-lactones with basic methanol, provided that the carboxyl group at C-2 of the oxetane is *trans* to the oxygen substituent at C-3.[38] The divergent oxetane acetal **8** can be prepared from D-xylose **7** by nucleophilic displacement by the hydroxyl function at C-4 of a triflate at C-2; C-1 must be oxidised to an acid with both the hydroxyl groups at C-3 and C-5 protected to prevent the competitive formation of three- or five-membered rings (Scheme 2).

Initial bromine oxidation of D-xylose **7** with barium carbonate and bromine in water[39] gave a crude product, which was subsequently reacted with benzaldehyde in concentrated hydrochloric acid to afford the crystalline benzylidene lactone **13**[40,41] in 51% yield (Scheme 2). Lactone **13**, with all the oxygen functionality protected other than the C-2 OH group, was esterified with trifluoromethanesulfonic (triflic) anhydride in dichloromethane in the presence of pyridine to give the corresponding triflate **14** in 90% yield. When **14** was treated with methanol containing potassium carbonate, the C-4 OH in the resulting open chain ester induced intramolecular ring closure to form the oxetane ester **8**



Scheme 2. Reagents and conditions: (i) Br_2, K_2CO_3, H_2O, −20 °C to rt; (ii) PhCHO, conc. HCl, rt (51% over 2 steps); (iii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 to −10 °C (90%); (iv) K_2CO_3, MeOH, −30 to −20 °C, (75%); (v) *p*-Me·$C_6H_4SO_3H$, MeOH, rt (92%); (vi) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 0 °C to rt (83%); (vii) *N*-bromosuccinimide, $BaCO_3$, CCl_4 (81%).

in 75% yield. The overall yield of the key divergent intermediate **8** from the protected xylonolactone **13** was 68%.

Acid catalysed methanolysis of **8** gave diol **12**, suitable for the protection of the primary position by silyl groups, in 92% yield. Alternatively, treatment of **8** with triethylsilane[42] in the presence of trifluoroacetic acid resulted in a highly regioselective reduction to form the 5-*O*-benzyl ether **9** in which only the secondary alcohol of the oxetane ring is unprotected (83% yield). Bromination of the benzylidene acetal **8** under Hanessian–Hullar conditions[43] with *N*-bromosuccinimide also proceeded with highly regioselective ring opening to afford the bromomethyl derivative **11**. The oxetanes **9**, **11** and **12** with the C-3 OH free can then be further elaborated to give the target 3-azido-2-carboxylates.

2.2. Synthesis of benzyl protected *trans*-2 and *cis*-4 β-azido oxetane carboxylates

The synthesis of the *cis* and *trans* isomers of the benzyl-protected *cis*-**4** and *trans*-**2** azidoesters relied on highly efficient S_N2 displacements of the activated 3-hydroxyl group in the oxetane ring; all of the following examples of this procedure occurred in high yield without any competing elimination reactions (Scheme 3).

Esterification of the secondary alcohol in **9** by treatment with trifluoromethanesulfonic (triflic) anhydride in the presence of pyridine afforded the corresponding triflate **15**. Subsequent azide displacement with inversion of configuration gave the 2,3-*cis* azido ester **4** in an overall yield from **9** of 91%. Inversion of the hydroxyl group at C-3 prior to introduction of the azide allowed access to the 2,3-*trans* azide **2**. Triflate **15**, when refluxed with caesium trifluoroacetate in 2-butanone, generated the inverted alcohol **16** in 99% yield. Esterification of alcohol **16** gave the corresponding triflate **17**, which on subsequent azide displacement afforded the 2,3-*trans* azido ester monomer unit **2** in an overall yield of 84%.

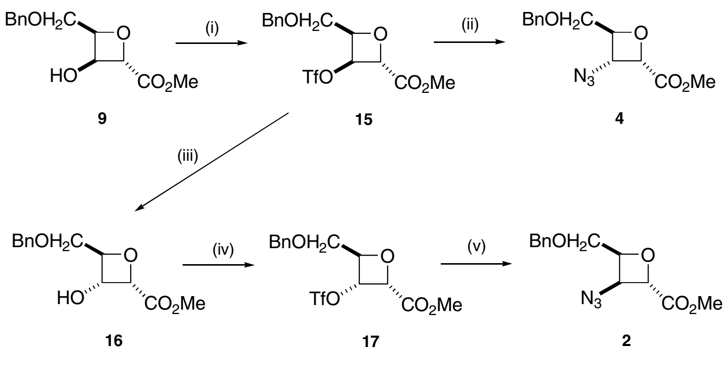
2.3. Synthesis of silyl protected *trans*-3 and *cis*-5 β-azido oxetane carboxylates

The use of silyl protecting groups as alternatives to benzyl ethers was also studied in order to both provide scaffolds with readily removable protecting groups and also to allow study of the secondary structural preferences of protected and unprotected oligomers in solution (Scheme 4). Again all the S_N2 reactions at the secondary alcohol of the oxetane proceeded in excellent yield. Initially the *tert*-butyldimethylsilyl (TBDMS) protecting group was selected, since the lack of a significant ultraviolet chromophore would allow circular dichroism to be used as a technique for structural investigation of the oligomeric materials.

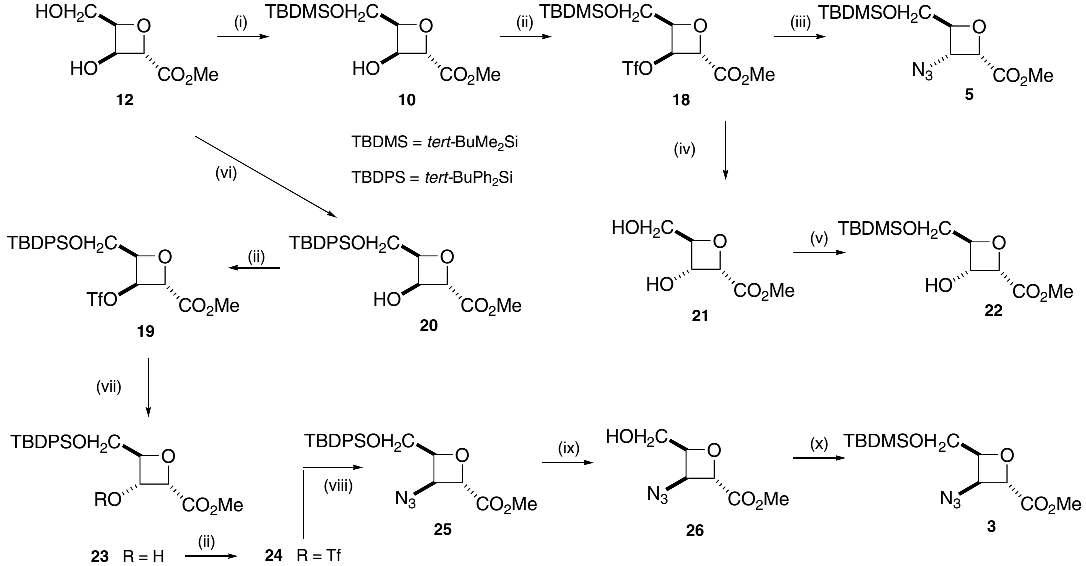
Highly regioselective selective protection of the primary hydroxyl group in **12** with TBDMS chloride in pyridine gave the monosilylated oxetane **10** in 93% yield. Esterification of the remaining alcohol in **10** with triflic anhydride and pyridine in dichloromethane afforded triflate **18**; subsequent treatment with sodium azide in DMF gave the inverted *cis*-azidoester **5** in 94% overall yield.

For the β-*trans*-framework **3** a double inversion of the C-3-OH function in the oxetane was again required. The S_N2 displacements in this system were consistently high yielding and efficient. However, the lability of the TBDMS ether during the epimerisation of the alcohol was problematic. Treatment of triflate **18** (protected as the TBDMS ether) with caesium trifluoroacetate in 2-butanone gave diol **21** as the major product (67% over two steps, Scheme 4). Attempts to selectively reprotect this inverted diol **21** using a number of conditions resulted in an optimised yield of **22** of only 35%. As the diol could not be selectively reprotected in a sufficiently good yield, the epimerisation of the alcohol at C-3 of the oxetane was undertaken using the more stable *tert*-butyldiphenylsilyl (TBDPS) protecting group.[44]

Selective protection of diol **12** with TBDPS chloride and imidazole in DMF afforded **20** in 91% yield. Sequential esterification of **20** with triflic anhydride to triflate **19**, followed by reaction with trifluoroacetate, gave the inverted TBDPS epimer **23** (88% over 2 steps). Esterification of **23** to triflate **24**, followed by reaction with sodium azide gave *trans*-azido ester **25** (83% over 2 steps). Exchange of the TBDPS for a TBDMS group as a non UV active protecting group was achieved by an initial reaction of **25** with acetyl chloride in methanol to give the primary alcohol **26**; subsequent treatment of **26** with TBDMS triflate in pyridine gave the



Scheme 3. Reagents and conditions: (i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 to −10 °C (97%); (ii) NaN_3, DMF, rt (93%); (iii) $CsOCOCF_3$, MeCOEt, 60 °C (99%); (iv) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 to −10 °C (98%); (v) NaN_3, DMF, rt (86%).



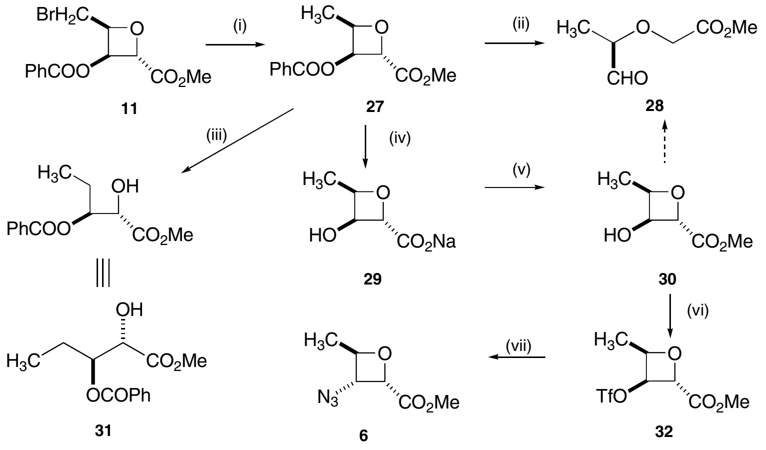
Scheme 4. Reagents and conditions: (i) TBDMSCl, pyridine, 0 °C to rt (93%); (ii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 to −10 °C; (iii) NaN_3, DMF, rt (94% over 2 steps); (iv) $CsOCOCF_3$, MeCOEt, 60 °C (67% over 2 steps); (v) TBDMSCl, pyridine, 0 °C to rt (35%); (vi) TBDPSCl, imidazole, DMF, −20 °C to rt (91%); (vii) $CsOCOCF_3$, MeCOEt, 60 °C (88% over 2 steps); (viii) NaN_3, DMF, rt (83% over 2 steps); (ix) AcCl, MeOH (76%); (x) TBDMSOTf, pyridine, −20 to 0 °C (99%).

target *trans*-azido ester scaffold **3** in 75% yield over 2 steps.

2.4. Synthesis of 4-methyl-*cis*-β-azido oxetane carboxylate 6

Hydrogenation of primary bromide **11** in the presence of palladium and sodium acetate did not lead to the required methyl oxetane **27** (Scheme 5); the major product **31**, the structure of which is consistent with the NMR spectrum, arose from the hydrogenolysis of both the oxetane ring and the bromoalkyl function. In contrast, radical dehalogenation of **11** by tris(trimethylsilyl)silane[45] in the presence of azobis(*iso*butyronitrile) [AIBN] in toluene gave the methyl oxetane **27** as the major product (56% yield).

Deprotection of 3-*O*-benzoyl derivatives of 3-hydroxyoxetane-2-carboxylate esters (such as **27**) by sodium methoxide in methanol was accompanied by a reverse aldol reaction to form the ring opened aldehydes, such as **28**. However the ring opening reaction can be prevented by the hydrolysis of both ester functions with sodium hydroxide, and subsequent re-esterification of the resulting sodium salt. Accordingly, benzoate ester **27** was treated with sodium hydroxide in aqueous THF to afford the sodium salt **29** which, on further reaction with hydrogen chloride in methanol, gave the required methyl ester **30** in satisfactory yield (78% over 2 steps). Alcohol **30** was converted to triflate **32** with triflic anhydride and pyridine (94%) and subsequent reaction of **32** with sodium azide in DMF gave the target methyl β-azido ester **6** in good yield (92%). The overall yield of



Scheme 5. Reagents and conditions: (i) AIBN, $(Me_3Si)_3SiH$, toluene, 60 °C (56%); (ii) NaOMe, MeOH, rt; (iii) 10% Pd/C, H_2, EtOAc, NaOAc, 5 atm; (iv) NaOH, THF, H_2O, rt; (v) conc. HCl, MeOH, rt (78% over two steps); (vi) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (94%); (vii) NaN_3, DMF (92%).

the methyl analogue of oxetin **6** from the bromomethyl ester **11** compound was 38% over 5 steps.

3. Conclusion

This paper describes the preparation of a series of 2,3-*cis* and -*trans* β-azidoesters as new peptidomimetics and as analogues of the natural antibiotic oxetin. These syntheses depend on the consistent high yield of S_N2 nucleophilic displacements of triflates by oxygen and nitrogen nucleophiles in the oxetane ring, which are β to esters. It is noteworthy that there are no competing elimination reactions in this system. The following paper describes the synthesis of other oxetane β-amino acids derived from L-rhamnose.[46]

Preliminary studies by NMR have shown that the oligomers derived from *cis* β-azidoesters display an unprecedented 10-helix secondary structure stabilised by inter-residue hydrogen bonding (rather than six-membered intra-residue hydrogen bonding). This is in marked contrast to that found for cyclohexane-, cyclopentane- and pyrrolidine-oligomers reported elsewhere.[8] NMR and circular dichroism studies of homooligomers of *cis*- and *trans*-β-amino acids derived from the azidoesters from D-xylose and L-rhamnose 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 (DMF) 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). Imidazole was recrystallised from dichloromethane. 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. ^{13}C multiplicities were assigned using a DEPT sequence. 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. (*S*)-3,5-*O*-Benzylidene-*D*-xylono-1,4-lactone 13

A solution of D-xylose **7** (20.0 g, 0.13 mol) in water (54 mL) was cooled in an ice water bath. Potassium carbonate (22.6 g, 0.16 mol) was then added in portions while keeping the temperature below 20 °C. The mixture was cooled to 5 °C and bromine (8 mL, 0.15 mol) added dropwise over 45 min while keeping the temperature below 10 °C. The resulting orange solution was stirred at 10 °C for 30 min and then at room temperature overnight, after which one major product was see by TLC (R_f 0.42, 9:1, ethyl acetate/methanol). The reaction was quenched by careful addition of 88% formic acid (1.66 mL) to give a colourless solution. The solution was concentrated at 50 °C in vacuo. Acetic acid (13.4 mL) was added and the mixture concentrated at 50 °C again to remove any residual water. This yielded the crude xylono-1,4-lactone, which was used without purification. To a solution of the crude lactone (assumed 19.7 g, 0.13 mol) in benzaldehyde (200 mL) was added conc. hydrochloric acid (15 mL). The reaction was stirred at room temperature overnight, to give one major product (R_f 0.4, 1:1, ethyl acetate/hexane). The mixture was concentrated under reduced pressure to 1/4 volume. Ether (80 mL) was added and a precipitate formed. The mixture was filtered and the residue washed with ether. The filtrate was concentrated in vacuo, columned (1:2, ethyl acetate/hexane) and recrystallised from ethyl acetate/hexane to give the benzylidene protected lactone **13** as a white crystalline solid (19.0 g, 60% yield over two steps). HRMS m/z (CI+): found 237.0765 ($M+H^+$); $C_{12}H_{13}O_5$ requires 237.0763; mp 124–126 °C, (lit.[40] mp 124–126 °C); $[\alpha]_D^{22} = +70.2$ (c, 1.01 in acetone), {lit.[40] $[\alpha]_D^{20} = +63.3$ (c, 1.0 in acetone)}; ν_{max} (thin film): 3100–3600 (m, br, OH), 1774 (s, C=O); δ_H (d_6-acetone, 400 MHz): 4.18 (1H, d, H2, J 4.6), 4.38 (1H, dd, H5, J

13.9, 1.7), 4.51 (1H, d, H5′, *J* 13.9), 4.69–4.74 (2H, a-s, H3, H4), 5.74 (1H, s, **C**HPh), 5.79 (1H, d, 2-OH, *J* 4.6), 7.36–7.43 (3H, m, ArH), 7.44–7.50 (2H, m, ArH); δ_C (d_6-acetone, 50 MHz): 66.5 (C5), 73.8 (C2 and (C3 or C4)), 77.7 (C3 or C4), 99.1 (**C**HPh), 126.6 (ArCH), 128.4 (ArCH), 129.3 (ArCH), 138.5 (ArC), 175.1 (C=O); *m*/*z* (APCI+ve) 237 (M+H$^+$, 20%) 121 (100%).

4.2. (*S*)-3,5-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone 14

A solution of benzylidene lactone **13** (3.15 g, 13.36 mmol) and pyridine (3.24 mL, 40.09 mmol) in dichloromethane (19 mL) was cooled to −30 °C. Trifluoromethanesulfonic (triflic) anhydride (3.6 mL, 21.38 mmol) was added dropwise and the reaction stirred for 2.25 h at −30 to −10 °C, when one major product was formed (R_f 0.7, 1:1, ethyl acetate/hexane). The reaction mixture was diluted with dichloromethane (80 mL) and washed with 2 M hydrochloric acid (40 mL). The aqueous layer was further extracted with dichloromethane (3 × 50 mL), washed with brine (80 mL), dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by column chromatography (1:3, ethyl acetate/hexane) to give the triflate **5** (4.74 g, 96%) as a white solid. Mp 93–95 °C [lit.[40] mp 94–96 °C]; $[\alpha]_D^{22} = +63.5$ (*c*, 0.89 in acetone), {lit.[40] $[\alpha]_D^{20} = +63.6$ (*c*, 1.0 in acetone)}; ν_{max} (thin film): 1803 (s, C=O); δ_H (d_6-acetone, 400 MHz): 4.52 (1H, dd, H5, *J* 14.1, 2.0), 4.62 (1H, d, H5′, *J* 14.0), 5.04 (1H, m, H4), 5.33 (1H, d, H3, *J* 2.5), 5.41 (1H, s, H2), 5.90 (1H, s, **C**HPh), 7.40–7.44 (3H, m, ArH), 7.48–7.53 (2H, m, ArH); δ_C (d_6-acetone, 100 MHz): 66.8 (C5), 75.6 (C3, C4), 82.8 (C2), 100.4 (**C**HPh), 119.7 (CF_3 q, *J* ^{13}C–^{19}F 322 Hz), 127.5 (ArCH), 129.5 (ArCH), 130.5 (ArCH), 138.6 (ArC), 168.8 (C=O); *m*/*z* (APCI+ve): 369 (M+H$^+$, 5%), 195 ($C_{11}H_{15}O_3^+$, 100%).

4.3. Methyl 2,4-anhydro-(*S*)-3,5-*O*-benzylidene-D-lyxonate 8

A solution of triflate **14** (4.76 g, 0.013 mol) in methanol (730 mL) was cooled to −23 °C. Potassium carbonate (3.21 g, 0.023 mol) was added in one portion and the reaction stirred for 4 h while keeping the temperature between −25 and −20 °C. After that time, complete conversion to one major product was seen (R_f 0.5, 1:1, ethyl acetate/hexane). The mixture was filtered through silica and eluted with methanol. It was then concentrated under reduced pressure and purified by column chromatography (1:3, ethyl acetate/hexane) to give oxetane **8** (2.43 g, 75%). HRMS *m*/*z* (CI+): found 251.0924 (M+H$^+$); $C_{13}H_{15}O_5$ requires 251.0919; mp 121–126 °C (lit.[40] mp 122–124 °C); $[\alpha]_D^{22} = -30.5$ (*c*, 0.98 in $CHCl_3$), {lit.[40] $[\alpha]_D^{20} = -28.2$ (*c*, 1.0 in $CHCl_3$)}; ν_{max} (thin film): 1732 (s, C=O); δ_H (d_6-acetone, 400 MHz): 3.79 (3H, s, OMe), 4.16 (1H, dd, H5, *J* 13.9, 2.6), 4.24 (1H, d, br, H5′, *J* 13.9), 4.64 (1H, dd, H2, *J* 2.3, 1.0), 4.96 (1H, dddd, H4, *J* 5.1, 2.6, 0.9, 0.9), 5.04 (1H, dd, H3, *J* 5.1, 2.3), 5.62 (1H, s, CHPh), 7.39–7.45 (3H, m, ArH), 7.54–7.57 (2H, m, ArH); δ_C (d_6-acetone, 100 MHz): 52.8 (OCH_3), 70.3 (C5), 74.1 (C3), 76.4 (C4), 85.1 (C2), 98.8 (**C**HPh), 127.6 (ArCH), 129.3 (ArCH). 130.0 (ArCH), 140.1 (ArC), 171.3 (C=O); *m*/*z* (APCI+ve): 251 (M+H$^+$, 20%), 121 ($C_8H_9O^+$, 100%).

4.4. Methyl 2,4-anhydro-D-lyxonate 12

The benzylidene protected oxetane **8** (1.06 g, 4.24 mmol) was stirred in methanol (10 mL) and *para*-toluenesulfonic acid (cat.) then added. The reaction was stirred at room temperature for 1 h when TLC (ethyl acetate) showed complete conversion of the starting material (R_f 0.9) to one major spot (R_f 0.41). The solution was neutralised with solid sodium bicarbonate, filtered through Celite and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (2:1, ethyl acetate/hexane) to yield oxetane diol **12** as a white crystalline solid (628 mg, 92%). mp 38–40 °C; $[\alpha]_D^{24} = -27.1$ (*c*, 0.92 in $CHCl_3$); ν_{max} (thin film): 3392 (br, s, OH), 1739 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 3.12 (1H, dd, 5-O**H**, *J* 4.8, 7.3), 3.82 (3H, s, OMe), 4.04 (1H, ddd, H5, *J* 1.3, 7.3, 13.3) 4.10 (1H, ddd, H5′, *J* 2.6, 4.5, 13.3), 4.50 (1H, d, 3-O**H**, *J* 10.4), 4.80–4.90 (2H, m, H3, H4), 5.09 (1H, d, H2, *J* 4.8); δ_C ($CDCl_3$, 100 MHz): 52.4 (O**C**H_3), 62.8 (C5), 71.5 (C3), 85.2 (C4), 87.5 (C2), 170.7 (C=O); *m*/*z* (APCI+ve): 180 (M+NH_4^+, 100%), 163 (M+H$^+$, 20%).

4.5. Methyl 2,4-anhydro-5-*O*-benzyl-D-lyxonate 9

Triethylsilane (1.6 mL, 0.01 mol) was added to a solution of benzylidene acetal **8** (500 mg, 2 mmol) in dichloromethane (5 mL) and the reaction mixture cooled to 0 °C. Trifluoroacetic acid (0.77 mL, 0.01 mol) was then added dropwise and the reaction allowed to warm to room temperature. After 3 h, complete conversion of starting material (R_f 0.67) to one major product (R_f 0.56) was seen by TLC (2:1, ethyl acetate/hexane). The mixture was diluted with ethyl acetate (50 mL) washed with sodium bicarbonate (aq, 20 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated. The resulting product was purified by flash column chromatography (1:3, ethyl acetate/hexane) to yield secondary alcohol **7** as a white crystalline solid (418 mg, 83% yield). Found: C, 61.92; H, 6.17; $C_{13}H_{16}O_5$ requires: C, 61.90; H, 6.39; mp 62–63 °C (ethyl acetate/hexane); $[\alpha]_D^{25} = -5.6$ (*c*, 0.9 in $CHCl_3$); ν_{max} (thin film): 3449 (OH, br), 1738 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.81 (3H, s, OMe), 3.99 (2H, d, H5, H5′, *J* 1.93), 4.35–4.55 (1H, br, OH), 4.63 (1H, d, C**H**Ph, *J* 11.8), 4.73 (1H, d, C**H**′Ph, *J* 11.8), 4.80 (1H, m, H3), 4.86 (1H, m, H4), 5.14 (1H, d, H2, *J* 5.4), 7.38 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 52.2 (O**C**H_3), 70.8 (C5), 71.45 (C3), 74.3 (**C**H_2Ph), 84.4 (C4), 87.4 (C2), 127.8 (ArCH), 128.2 (ArCH), 128.6 (ArCH), 136.8 (ArC), 170.7 (C=O); *m*/*z* (APCI+ve): 275 (M+Na$^+$, 5%) 253 (M+H$^+$, 5%), 122 (100%).

4.6. Methyl 2,4-anhydro-3-*O*-benzoyl-5-bromo-5-deoxy-D-lyxonate 11

N-Bromosuccinimide (1.29 g, 7.26 mmol) and barium carbonate (0.677 g, 3.43 mmol) were added to a solution of benzylidene oxetane **8** (1.65 g, 6.6 mmol) in CCl_4

(44.5 mL) and $BaCO_3$. The reaction was stirred at 60 °C overnight after which complete conversion of the starting material to one major product (R_f 0.56, 1:2 ethyl acetate/hexane) was seen. The reaction mixture was diluted with DCM (100 mL), washed with brine (100 mL) and diluted with water (150 mL) to dissolve the precipitate formed. The aqueous layer was further extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by column chromatography (1:7 ethyl acetate/hexane) to give bromide **11** as a light yellow oil (1.06 g, 81% yield). Found: C 47.31; H 3.99; $C_{13}H_{13}O_5Br$ requires: C 47.44; H 3.98; HRMS *m*/*z* (CI+): found 329.0035 ($M+H^+$); $C_{13}H_{14}O_5$ Br requires 329.0025; $[\alpha]_D^{22} = -10.5$ (*c*, 1.025 in $CHCl_3$); ν_{max} (thin film): 1728 (s, br, C=O); δ_H ($CDCl_3$, 400 MHz): 3.67 (1H, dd, H5, *J* 10.5, 6.6), 3.77 (1H, dd, H5′, *J* 10.5, 7.4), 5.17 (1H, d, H2, *J* 4.8), 5.25 (1H, dd, H4, *J* 6.6, 7), 5.87 (1H, dd, H3, *J* 6.2, 4.8), 7.45–7.52 (2H, m, *m*-ArH), 7.64 (1H, m, *p*-ArH), 8.10 (2H, m, *o*-ArH); δ_C ($CDCl_3$, 50.3 MHz): 28.7 (C5), 53.3 (OCH_3), 70.0 (C3), 82.3 (C2), 82.6 (C4), 128.9 (ArC), 129.2 (*m*-ArCH), 130.4 (*o*-ArCH), 134.4 (*p*-ArCH), 165.6 (Ph**C**=O), 169.8 (C=O); *m*/*z* (APCI+ve): 353 ($M+Na^{+81}Br$, 2%), 331 ($M+H^{+81}Br$, 18%), 329 ($M+H^{+79}Br$, 20%), 122 (100%).

4.7. Methyl 2,4-anhydro-5-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-D-lyxonate 15

A solution of alcohol **9** (978 mg, 3.88 mmol) in dichloromethane (6.5 mL) in the presence of pyridine (0.94 mL, 11.6 mmol) was cooled to −30 °C and triflic anhydride (1.05 mL, 6.21 mmol) then added dropwise. The reaction was stirred at −30 °C to −10 °C for 45 min when complete conversion to one major product was seen by TLC (R_f 0.85, 2:1, ethyl acetate/hexane). The solution was diluted with dichloromethane (100 mL) and washed with 2 M hydrochloric acid (40 mL). The aqueous layer was further extracted with dichloromethane (3 × 30 mL) and the organic layers then combined and washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (1:3, ethyl acetate/hexane) to give triflate **15** as a white crystalline solid (1.44 g, 97%). Found: C, 43.80, H, 3.92, $C_{14}H_{15}F_3O_7S$ requires: C, 43.75, H, 3.93; mp 29–31 °C; $[\alpha]_D^{23} = +24.6$ (*c*, 1.06 in $CHCl_3$); ν_{max} (thin film): 1750.5 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.84 (1H, dd, H5, *J* 11.0, 4.6), 3.86 (3H, s, OMe), 3.96 (1H, dd, H5′, *J* 11.0, 5.7), 4.59 (1H, d, C**H**Ph, *J* 11.8) 4.66 (1H, C**H**′Ph, *J* 11.8), 5.05–5.1 (1H, m, H4), 5.26 (1H, dd, H2, *J* 5.1, 1.1), 5.68–5.75 (1H, a-t, H3, *J* 5.8), 7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 52.9 (**O**CH_3), 67.4 (C5), 73.8 (**C**H_2Ph), 78.5 (C3), 81.5 (C2), 81.7 (C4), 127.8 (ArCH), 127.9 (ArCH), 128.5 (ArCH), 137.2 (ArC). 168.0 (C=O); *m*/*z* (APCI+ve): 402 ($M+NH_4^+$, 100%), 384 ($M+H^+$, 14%).

4.8. Methyl 2,4-anhydro-3-azido-5-*O*-benzyl-3-deoxy-D-arabinonate 4

Sodium azide (365 mg, 5.62 mmol) was added in one portion to a solution of triflate **15** (1.44 g, 3.75 mmol) in DMF (42 mL). The reaction mixture was stirred at room temperature for 1.5 h after which no starting material and one major product were seen by TLC (R_f 0.8, 2:1, ethyl acetate/hexane). A few drops of water were added and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (120 mL) and washed with brine (60 mL). The aqueous layer was then extracted with ethyl acetate (3 × 40 mL). The ethyl acetate layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude azide was purified by flash chromatography (1:3, ethyl acetate/hexane) to give the *cis*-azide **4** as a colourless oil (986 mg, 93% yield). Found: C, 56.07, H, 5.63, N, 14.74; $C_{13}H_{15}N_3O_4$ requires: C, 56.31, H, 5.45, N, 15.15; $[\alpha]_D^{25} = +128.8$ (*c*, 1.05 in $CHCl_3$); ν_{max} (thin film); 2116 (N_3), 1756 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.67 (1H, dd, H5, *J* 11.9, 2.9), 3.72 (1H, dd, H5′, *J* 11.9, 3.0), 3.89 (3H, s, OMe), 4.61 (1H, d, C**H**Ph, *J* 12.1), 4.69 (1H, d, C**H**′Ph, *J* 12.1), 4.79–4.81 (1H, m, H4), 4.93 (1H, dd, H3, *J* 7.6, 5.6), 5.22 (1H, d, H2, *J* 7.6), 7.29–7.41 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 52.3 (**O**CH_3), 56.7 (C3), 69.4 (C5), 73.8 (**C**H_2Ph), 79.4 (C2), 86.2 (C4), 127.7 (ArCH), 127.9 (ArCH), 128.5 (ArCH), 137.6 (ArC), 169.4 (C=O); *m*/*z* (APCI+ve): 295 ($M+NH_4^+$, 35%), 250 ($M+H^+-N_2$, 100%).

4.9. Methyl 2,4-anhydro-5-*O*-benzyl-D-arabinonate 16

Caesium trifluoroacetate (2.64 g, 12.0 mmol) was added in one portion to a solution of oxetane triflate **15** (1.03 g, 2.68 mmol) in butanone (30 mL); the reaction mixture was stirred at 60 °C for 16 h when the starting material (R_f 0.85) had been converted to one major product (R_f 0.48, 2:1, ethyl acetate/hexane). The reaction was concentrated under reduced pressure and purified by flash chromatography (2:1, hexane/ethyl acetate) to give the inverted alcohol **16** as a white crystalline solid (671 mg, 99%). Found: C, 61.59, H, 6.30; $C_{13}H_{16}O_5$ requires: C, 61.90, H, 6.39; mp 83–84 °C (ethyl acetate/hexane); $[\alpha]_D^{24} = -17.2$ (*c*, 1.04 in $CHCl_3$); ν_{max} (thin film): 3445 (OH, br), 1739 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.05 (1H, br, OH), 3.65–3.75 (2H, m, H5, H5′), 3.85 (3H, s, OMe), 4.58 (1H, d, C**H**Ph, *J* 12.0), 4.66 (1H, d, C**H**′Ph, *J* 12.0), 4.88–4.92 (1H, m, H4), 4.96 (1H, dd, H3, *J* 6.9, 5.2), 5.11 (1H, d, H2, *J* 6.9), 7.25–7.4 (5H, m, ArH); δ_c ($CDCl_3$, 100.6 MHz): 52.3 (**O**CH_3), 67.4 (C3), 69.6 (C5), 73.6 (**C**H_2 Ph), 81.9 (C2), 89.7 (C4), 127.7 (ArCH), 127.8 (ArCH), 128.4 (ArCH), 137.8 (ArC), 170.7 (C=O); *m*/*z* (APCI+ve): 275 ($M+Na^+$, 7%), 270 ($M+NH_4^+$, 5%), 253 ($M+H^+$, 25%), 145 (100%).

4.10. Methyl 2,4-anhydro-5-*O*-benzyl-3-trifluoromethanesulfonyl-D-arabinonate 17

Triflic anhydride (0.30 mL, 1.8 mmol) was added dropwise to a solution at −30 °C of the alcohol **16** (283 mg, 1.12 mmol) in dichloromethane (2.4 mL) in the presence of pyridine (0.27 mL, 3.37 mmol). The reaction mixture was stirred at −30 °C to −10 °C for 1 h after which no starting material (R_f 0.4) and one major product (R_f 0.9) were seen by TLC (1:1, ethyl acetate/hexane).

Dichloromethane (30 mL) was added and the solution was washed with 2 M hydrochloric acid (10 mL). The aqueous layer was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were then washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (1:3, ethyl acetate/hexane) to give triflate **11** as an oil (423 mg, 98%). Found: C, 43.87, H, 3.89; $C_{14}H_{15}F_3O_7S$ requires: C, 43.75, H, 3.93; $[\alpha]_D^{24} = +33.1$ (*c*, 0.86 in $CHCl_3$); ν_{max} (thin film): 1766 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.67 (1H, dd, H5, *J* 12.2, 2.4), 3.74 (1H, dd, H5′, *J* 12.2, 2.3), 3.88 (3H, s, OMe), 4.61 (1H, d, C**H**Ph, *J* 12.1), 4.71 (1H, d, C**H**′Ph, *J* 12.1), 5.1–5.14 (1H, m, H4), 5.26 (1H, dd, H2, *J* 7.1, 1.0), 5.89 (1H, dd, H3, *J* 7.0, 5.0), 7.3–7.45 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz): 52.7 (O**C**H$_3$), 67.9 (C5), 73.8 (**C**H$_2$Ph), 76.6 (C3), 78.5 (C2), 86.5 (C4), 127.7 (ArCH), 128.0 (ArCH), 128.5 (ArCH), 137.2 (ArC), 167.3 (C=O); *m/z* (APCI+ve): 402 (M+NH$_4^+$, 100%).

4.11. Methyl 2,4-anhydro-3-azido-5-*O*-benzyl-3-deoxy-D-lyxonate 2

Sodium azide (107 mg, 1.65 mmol) was added in one portion to a solution of the triflate **17** (423 mg, 1.1 mmol) in DMF (12.7 mL); the reaction mixture was stirred at room temperature for 3.5 h after which TLC showed complete conversion to one major product (R_f 0.85, 1:1, ethyl acetate/hexane). A few drops of water were added and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (60 mL) and washed with brine (30 mL). The aqueous layers were further extracted with ethyl acetate (3 × 30 mL) and the combined organic layers dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3:1, hexane/ethyl acetate) to give the *trans*-azide **2** as a colourless oil (263 mg, 86%). Found: C 56.11, H 5.81, N 14.68; $C_{13}H_{15}N_3O_4$ requires: C 56.31, H 5.45, N 15.15; $[\alpha]_D^{26} = +44.1$ (*c*, 0.95 in $CHCl_3$); ν_{max} (thin film): 2112 (N_3), 1760 (C=O); δ_H ($CDCl_3$, 400 MHz): 3.78 (1H, dd, H5, *J* 10.8, 5.1), 3.85 (3H, s, OMe), 3.91 (1H, dd, H5′, *J* 10.8, 6.0), 4.62 (2H, s, C**H**$_2$Ph), 4.71–4.74 (1H, m, H3), 4.96–5.01 (2H, m, H2, H4), 7.3–7.45 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 52.6 (O**C**H$_3$), 58.8 (C3), 68.6 (C5), 73.7 (**C**H$_2$Ph), 81.6 (C2), 81.8 (C4), 127.8 (2 × ArCH), 128.4 (3 × ArCH), 137.6 (ArC), 170.0 (C=O); *m/z* (APCI+ve): 250 (M+H$^+$−N$_2$, 75%), 144 (100%).

4.12. Methyl 2,4-anhydro-5-*O*-*tert*butyldimethylsilyl-D-lyxonate 10

TBDMS chloride (909 mg, 6.03 mmol) was added to a solution of diol **12** (850 mg, 5.24 mmol) in pyridine (11 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight when one major spot was seen (R_f 0.83, 1:1, ethyl acetate/hexane). The solution was evaporated under reduced pressure and the resulting crude mixture purified by column chromatography on neutral alumina (1:2, ethyl acetate/hexane) to yield the pure monosilylated ether **10** as a colourless oil (1.353 g, 93%). Found: C, 52.18, H, 8.69; $C_{12}H_{24}O_5Si$ requires: C, 52.14, H, 8.75; $[\alpha]_D^{24} = -9.7$ (*c*, 0.97 in $CHCl_3$); ν_{max} (thin film): 3466 (br, s, OH), 1748 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 0.15 (3H, d, SiC**H**$_3$, *J* 1.0), 0.17 (3H, d, SiC**H**$_3$, *J* 1.0), 0.95 (9H, d, SiC(C**H**$_3$)$_3$, *J* 1.4), 3.80 (3H, d, OMe, *J* 1.3), 4.09 (2H, s, H5), 4.77–4.82 (2H, m, H3, H4), 5.04 (1H, m, H2); δ_C ($CDCl_3$, 100 MHz): −5.7, −5.4 (2 × Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 52.2 (O**C**H$_3$), 64.6 (C5), 72.0 (C3), 84.8 (C4), 87.7 (C2), 170.8 (C=O); *m/z* (APCI+ve): 277 (M+H$^+$, 100%), 294 (M+NH$_4^+$).

4.13. Methyl 2,4-anhydro-5-*O*-*tert*butyldimethylsilyl-3-*O*-trifluoromethanesulfonyl-D-lyxonate 18

A solution of the TBDMS ether **10** (474 mg, 1.72 mmol) in dichloromethane (30 mL) and pyridine (0.42 mL, 5.15 mmol) was cooled to −30 °C and treated with triflic anhydride (0.46 mL, 2.75 mmol). The reaction mixture was stirred between −30 to −10 °C for 3 h after which the complete conversion of the starting material (R_f 0.18) to one major spot (R_f 0.5, 1:4, ethyl acetate/hexane) was seen. The reaction was diluted with dichloromethane (50 mL), washed with water (15 mL) and copper sulfate (aq, sat., 15 mL), then dried over magnesium sulfate and concentrated in vacuo. Triflate **18** was purified as a yellow oil (73 mg, 50%), for characterisation by column chromatography (neutral alumina, 1:4 ethyl acetate/hexane). [However, in subsequent reactions the crude triflate was used without further purification.] HRMS *m/z* (CI+): found 426.1230 (M+NH$_4^+$); $C_{13}H_{27}F_3NO_7SSi$ requires 426.1232, found 409.0964 (MH$^+$); $C_{13}H_{24}F_3O_7SSi$ requires 409.0976; $[\alpha]_D^{24} = +15.4$ (*c*, 0.85 in $CHCl_3$); ν_{max} (thin film): 1763 (br, m, C=O); δ_H ($CDCl_3$, 400 MHz): 0.10 (6H, s, 2 × SiC**H**$_3$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 3.86 (3H, s, OMe), 3.94 (1H, dd, H5, *J* 3.8, 11.7), 4.09 (1H, dd, H5′, *J* 5.7, 11.7), 4.88–4.92 (1H, m, H4), 5.27 (1H, d, H2, *J* 5.3), 5.69–5.72 (1H, a-t, H3, *J* 6.0); δ_C ($CDCl_3$, 100 MHz): −5.7, −5.7 (SiCH$_3$), 18.2 (Si**C**(CH$_3$)$_3$), 25.7 (SiC(**C**H$_3$)$_3$), 52.9 (O**C**H$_3$), 60.9 (C5), 78.4 (C3), 81.5 (C2), 82.9 (C4), 168.2 (C=O); *m/z* (APCI+ve): 426 (M+NH$_4^+$, 100%), 409 (M+H$^+$, 35%).

4.14. Methyl 2,4-anhydro-3-azido-5-*O*-*tert*butyldimethylsilyl-3-deoxy-D-arabinonate 5

Crude triflate **18** (0.7 g, 1.71 mmol) in DMF (20 mL) was treated with sodium azide (167 mg, 2.57 mmol). The reaction mixture was stirred at room temperature for 2 h after which TLC (1:4, ethyl acetate/hexane) showed the complete conversion of the starting material (R_f 0.5) to one major spot (R_f 0.7). The solution was concentrated in vacuo and the residue dissolved in ethyl acetate (80 mL) and the solution washed with brine (30 mL). The aqueous layer was further extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (neutral alumina, 1:5, ethyl acetate/hexane) to give the *cis*-azide **5** (484 mg, 94% over 2 steps) as a clear oil. Found: C, 47.89, H, 7.74, N, 13.95; $C_{12}H_{23}N_3O_4Si$ requires: C, 47.82, H, 7.69, N, 13.94;

$[\alpha]_D^{24} = +95.7$ (*c*, 1.27 in CHCl$_3$); ν_{max} (thin film): 2119 (s, N$_3$), 1766 (br, s, C=O); δ_H (CDCl$_3$, 400 MHz): 0.10 (3H, s, SiC**H**$_3$), 0.10 (3H, s, SiC**H**$_3$), 0.93 (9H, s, SiC(C**H**$_3$)$_3$), 3.75 (1H, dd, H5, *J* 2.4, 12.4), 3.83 (1H, dd, H5′, *J* 3.0, 12.4), 3.88 (3H, s, OMe), 4.67–4.70 (1H, m, H4), 4.86 (1H, dd, H3, *J* 5.4, 7.6), 5.12 (1H, d, H2, *J* 7.6); δ_C (CDCl$_3$, 100 MHz): −5.5, −5.4 (2 × Si**C**H$_3$), 18.3 (Si**C**(CH$_3$)$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 52.3 (O**C**H$_3$), 56.3 (C3), 62.8 (C5), 79.2 (C2), 87.2 (C4), 169.6 (C=O); *m*/*z* (APCI+ve): 274 (M+H$^+$−N$_2$, 15%), 142 (100%).

4.15. Methyl 2,4-anhydro-D-arabinonate 21

The crude silyl protected triflate **18** (823 mg, 2.0 mmol) in butanone (22.2 mL) was treated with caesium trifluoroacetate (1.99 g, 8.07 mmol) and added in one portion. The reaction was mixture was heated to 60 °C for 18 h after which TLC (ethyl acetate) showed the formation of one major product (R$_f$ 0.2). The solution was concentrated in vacuo and purified by column chromatography (ethyl acetate) to give diol **21**, recrystallised from ethyl acetate/methanol/hexane as a white solid (217 mg, 67% over 2 steps). Found: C, 44.52, H, 5.98; C$_6$H$_{10}$O$_5$ requires: C, 44.45, H, 6.22; HRMS *m*/*z* (CI+): found 163.0601 (M+H$^+$), C$_6$H$_{11}$O$_5$ requires 163.0606; mp 123–126 °C (from ethyl acetate/methanol/hexane); $[\alpha]_D^{26} = -5.7$ (*c*, 1.04 in MeOH); ν_{max} (thin film): 3444 (s, br, OH), 1788 (s, C=O); δ_H (CD$_3$CN, 400 MHz): 3.0–3.30 (2H, br, 2 × O**H**), 3.62–3.67 (1H, dd, H5, *J* 4.1, 13.0), 3.68–3.73 (1H, dd, H5′, *J* 3.5, 13.0), 4.65–4.69 (1H, m, H4), 4.81 (1H, dd, H3, *J* 5.3, 7.2), 5.05 (1H, dd, H2, *J* 0.6, 7.2); δ_C (CD$_3$CN, 100 MHz): 51.9 (O**C**H$_3$), 62.2 (C5), 66.8 (C3), 82.4 (C2), 91.4 (C4), 171.4 (C=O); *m*/*z* (CI+): 180 (M+NH$_4^+$, 100%), 163 (M+H$^+$, 30%).

4.16. Methyl 2,4-anhydro-5-*O*-*tert*butyldimethylsilyl-D-arabinonate 22

Diol **21** (60 mg, 0.37 mmol) in pyridine (0.8 mL) at 0 °C was treated with TBDMS chloride (64 mg, 0.43 mmol) and the reaction mixture allowed to warm to room temperature overnight when one major spot was seen (R$_f$ 0.59, 1:1, ethyl acetate/hexane). The solution was evaporated under reduced pressure; the resulting crude product purified by column chromatography on neutral alumina (1:2, ethyl acetate/hexane) to afford the pure monosilylated ether **22** as a white solid (36 mg, 35%). HRMS *m*/*z* (CI+): found 277.1471 (M+H$^+$), C$_{12}$H$_{25}$O$_5$Si requires 277.1474; mp 40–43 °C (from ethyl acetate/hexane); $[\alpha]_D^{26} = -21.6$ (*c*, 0.93 in CHCl$_3$); ν_{max} (thin film): 3437 (s, br, OH), 1738 (s, br, C=O); δ_H (CDCl$_3$, 400 MHz): 0.077 (3H, s, C**H**$_3$Si), 0.083 (3H, s, C**H**$_3$Si), 0.91 (9H, s, (C**H**$_3$)$_3$CSi), 3.19–3.21 (1H, br, d, OH, *J* 6.5), 3.75–3.79 (1H, dd, H5, *J* 2.7, 12.5), 3.80–3.84 (1H, m, H5′), 3.84 (3H, s, OMe), 4.73–4.76 (1H, m, H4), 4.94–4.99 (1H, m, H3), 5.05 (1H, d, H2, *J* 6.9); δ_C (CDCl$_3$, 100 MHz): −5.3, −5.5 (2 × **C**H$_3$Si), 18.3 ((CH$_3$)$_3$ **C**Si), 25.8 (3 × (**C**H$_3$)$_3$CSi), 52.2 (O**C**H$_3$), 62.8 (C5), 66.9 (C3), 81.8 (C2), 90.8 (C4), 170.8 (C=O); *m*/*z* (APCI+ve): 277 (M+H$^+$, 5%), 127 (100%).

4.17. Methyl 2,4-anhydro-5-*O*-*tert*butyldiphenylsilyl-D-lyxonate 20

Diol **12** (170 mg, 1.05 mmol) in DMF (3 mL) at −20 °C was treated with imidazole (86 mg, 1.26 mmol) and *tert*-butylphenylsilyl (TBDPS) chloride (0.29 mL, 1.1 mmol). The reaction mixture was stirred between −20 and 0 °C for 1 h and then left to stir at room temperature overnight. TLC (1:1, ethyl acetate/hexane) showed the conversion of the starting material (R$_f$ 0.07) to one major product (R$_f$ 0.67). The reaction was concentrated under reduced pressure and the residue purified by column chromatography (1:4, ethyl acetate/hexane) to yield monosilylated ether **20** (389 mg, 91%) as a colourless oil. HRMS *m*/*z* (CI+): found 418.2049 (M+NH$_4^+$), C$_{22}$H$_{32}$NO$_5$Si requires 418.2050; $[\alpha]_D^{25} = +3.0$ (*c*, 1.03 in CHCl$_3$), {lit.[47] $[\alpha]_D^{20} = +2.4$ (*c*, 1.25 in CHCl$_3$)}; ν_{max} (thin film): 3478 (m, br, OH), 1749 (s, C=O); δ_H (CDCl$_3$, 500 MHz): 1.11 (9H, s, (C**H**$_3$)$_3$CSi), 3.85 (3H, s, OMe), 4.04–4.08 (1H, dd, H5, *J* 1.3, 12.7), 4.14–4.17 (1H, dd, H5′, *J* 2.3, 12.7), 4.80–4.93 (2H, m, H3, H4), 5.26 (1H, d, H2, *J* 5.0), 7.40–7.50 (6H, m, ArH), 7.71–7.74 (2H, a-dd, ArH, *J* 1.4, 7.9), 7.77–7.80 (2H, a-dd, ArH, *J* 1.5, 7.9); δ_C (CDCl$_3$, 125 MHz): 18.9 ((CH$_3$)$_3$**C**Si), 26.7 ((**C**H$_3$)$_3$CSi), 52.2 (O**C**H$_3$), 65.1 (C5), 72.1 (C3), 84.8 (C4), 87.7 (C2), 127.9, 128.0 (ArCH), 130.0, 130.1 (ArCH), 131.1, 131.9 (ArC), 135.4, 135.7 (ArCH), 170.8 (C=O); *m*/*z* (APCI+ve): 418 (M+NH$_4^+$, 100%).

4.18. Methyl 2,4-anhydro-5-*O*-*tert*butyldiphenylsilyl-3-*O*-trifluoromethanesulfonyl-D-lyxonate 19

The TBDPS ether **20** (155 mg, 0.39 mmol) in dichloromethane (6.5 mL) and pyridine (0.09 mL, 1.16 mmol) was treated at −30 °C with triflic anhydride (0.1 mL, 0.62 mmol). The reaction mixture was stirred at −30 to −10 °C for 3 h after which TLC (1:1, ethyl acetate/hexane) showed complete conversion to one product (R$_f$ 0.92). The solution was diluted with dichloromethane (20 mL) and washed with 2 M hydrochloric acid (15 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL) and the organic layers combined, washed with brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (1:4, ethyl acetate/hexane) to afford triflate **19** as a colourless oil (159 mg, 77%). In subsequent reactions, the crude triflate was used without further purification. Found: C, 51.53, H, 5.49; C$_{23}$H$_{27}$O$_7$F$_3$SSi requires C, 51.87, H, 5.11; HRMS *m*/*z* (CI+): found 550.1555 (M+NH$_4^+$), C$_{23}$H$_{31}$NO$_7$F$_3$SSi requires 550.1543; $[\alpha]_D^{25} = +16.2$ (*c*, 0.97 in CHCl$_3$); ν_{max} (thin film): 1761 (s, C=O); δ_H (CDCl$_3$, 400 MHz): 1.08 (9H, s, (C**H**$_3$)$_3$CSi), 3.88 (3H, s, OMe), 3.89–3.93 (1H, dd, H5, *J* 3.3, 12.2), 4.08–4.13 (1H, dd, H5′, *J* 5.2, 12.2), 4.90–4.96 (1H, m, H4), 5.39 (1H, dd, H2, *J* 0.85, 5.5), 5.78 (1H, a-t, H3, *J* 6.1), 7.38–7.49 (6H, m, ArH), 7.70–7.76 (4H, m, ArH); δ_C (CDCl$_3$, 100 MHz); 19.1 ((CH$_3$)$_3$**C**Si), 26.6 ((**C**H$_3$)$_3$CSi), 52.9 (O**C**H$_3$), 61.6 (C5), 78.3 (C3), 81.7 (C2), 83.0 (C4), 118.4 (**C**F$_3$, q, *J* ^{13}C–^{19}F 321), 127.8 (ArCH), 129.9 (2 × ArCH), 132.4 (ArC), 135.6 (ArCH), 168.3 (C=O); *m*/*z* (APCI+ve): 550 (M+NH$_4^+$, 100%).

4.19. Methyl 2,4-anhydro-5-*O*-*tert*butyldiphenylsilyl-D-arabinonate 23

Crude triflate **19** (732 mg, 1.375 mmol) in butanone (15 mL) was treated with caesium trifluoroacetate (1.35 g, 5.5 mmol). The solution was heated at 60 °C for 18 h. TLC (1:1, ethyl acetate/hexane) showed the complete conversion of the starting material to one product (R_f 0.66). The reaction mixture was concentrated under reduced pressure and the crude alcohol purified by column chromatography (1:4, ethyl acetate/hexane) to yield the inverted alcohol **23** (484 mg, 88% over 2 steps) as a white solid. HRMS *m/z* (CI+): found 418.2052 ($M+NH_4^+$), $C_{22}H_{32}NO_5Si$ requires 418.2050; mp 108–110 °C (from ethyl acetate/hexane); $[\alpha]_D^{25} = -21.6$ (*c*, 1.03 in $CHCl_3$); ν_{max} (thin film): 3437 (m, br, OH), 1740 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.09 (9H, s, ($\mathbf{CH}_3)_3$CSi), 2.74 (1H, d, OH, *J* 6.6), 3.79–3.84 (1H, dd, H5, *J* 2.6, 12.4), 3.87 (3H, s, OMe), 3.88–3.93 (1H, dd, H5′, *J* 2.6, 12.4), 4.78–4.81 (1H, m, H4), 5.10–5.15 (1H, m, H3), 5.19 (1H, d, H2, *J* 6.9), 7.37–7.47 (6H, m, ArH), 7.69–7.73 (4H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 19.3 (($CH_3)_3$ **C**Si), 26.7 ((**C**$H_3)_3$CSi), 52.3 (O**C**H_3), 63.5 (C5), 67.2 (C3), 81.7 (C2), 90.8 (C4), 127.8 (2 × ArCH), 129.8 (2 × ArCH), 132.7, 133.2 (ArC), 135.5, 135.7 (ArCH), 170.7 (C=O); *m/z* (APCI+ve): 418 ($M+NH_4^+$, 20%), 162 (100%).

4.20. Methyl 2,4-anhydro-5-*O*-*tert*butyldiphenylsilyl-3-*O*-trifluoromethanesulfonyl-D-arabinonate 24

Inverted alcohol **23** (62 mg, 0.155 mmol) in dichloromethane (2.6 mL) and pyridine (0.038 mL, 0.465 mmol) was added and cooled to −30 °C after which point triflic anhydride (0.042 mL, 0.248 mmol) was added dropwise. The reaction was maintained at −30 to −10 °C for 1 h after which TLC (1:1, ethyl acetate/hexane) showed complete conversion to one product (R_f 0.96). The solution was diluted with dichloromethane (20 mL) and washed with 2 M hydrochloric acid (10 mL). The aqueous layer was further extracted with dichloromethane (3 × 5 mL) and the organic layers combined, washed with brine (10 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (1:4, ethyl acetate/hexane) to yield the triflate **24** as a colourless oil (71 mg, 86%). In subsequent reactions, the crude triflate was used without further purification. Found: C, 51.60, H, 5.19; $C_{23}H_{27}O_7F_3SSi$ requires C, 51.87, H, 5.11; HRMS *m/z* (CI+): found 550.1536 ($M+NH_4^+$), $C_{23}H_{31}NO_7F_3SSi$ requires 550.1543; $[\alpha]_D^{25} = +10.5$ (*c*, 1.05 in $CHCl_3$); ν_{max} (thin film): 1767 (C=O); δ_H ($CDCl_3$, 400 MHz): 1.10 (9H, s, ($\mathbf{CH}_3)_3$CSi), 3.78–3.82 (1H, dd, H5, *J* 2.0, 12.8), 3.91 (3H, s, OMe), 3.92–3.95 (1H, dd, H5′, *J* 2.1, 12.9), 5.07–5.09 (1H, m, H4), 5.32–5.34 (1H, dd, H2, *J* 0.8, 7.1), 6.04–6.07 (1H, dd, H3, *J* 4.9, 7.0), 7.39–7.48 (6H, m, ArH), 7.67–7.71 (4H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 19.3 (($CH_3)_3$ **C**Si), 26.7 ((**C**$H_3)_3$CSi), 52.8 (O**C**H_3), 62.4 (C5), 76.4 (C3), 78.5 (C2), 87.6 (C4), 116.8 (**C**F_3), 127.9 (2 × ArCH), 130.0, 130.1 (ArCH), 132.1, 132.4 (ArC), 135.4, 135.5 (ArCH), 167.4 (C=O); *m/z* (APCI+ve): 550 ($M+NH_4^+$, 100%).

4.21. Methyl 2,4-anhydro-3-azido-5-*O*-*tert*butyldiphenylsilyl-3-deoxy-D-lyxonate 25

Sodium azide (243 mg, 3.74 mmol) in DMF (29.7 mL) was added to the crude triflate **24** (1.325 g, 2.49 mmol) and the reaction mixture stirred at room temperature. After 18 h, TLC (1:2, ethyl acetate/hexane) showed complete conversion of the starting material (R_f 0.73) to one product (R_f 0.62). The reaction was concentrated under reduced pressure, the residue dissolved in ethyl acetate (100 mL) and washed with brine (50 mL). The aqueous layer was further extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (1:4, ethyl acetate/hexane) to yield the *cis*-azide **25** as a colourless oil (878 mg, 83% over 2 steps). HRMS *m/z* (CI+); found 443.2107 ($M+NH_4^+$), $C_{22}H_{31}N_4O_4Si$ requires 443.2115; $[\alpha]_D^{25} = +23.3$ (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 2112 (s, N_3), 1760 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.08 (9H, s, ($\mathbf{CH}_3)_3$CSi), 3.86 (3H, s, OMe), 3.88–3.92 (1H, dd, H5, *J* 6.1, 11.4), 4.07–4.10 (1H, dd, H5′, *J* 4.6, 11.5), 4.78–4.80 (1H, dd, H3, *J* 6.0, 7.0), 4.87–4.91 (1H, m, H4), 4.98 (1H, d, H2, *J* 5.8), 7.39–7.47 (6H, m, ArH), 7.70–7.74 (4H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 19.0 (($CH_3)_3$ **C**Si), 26.6 ((**C**$H_3)_3$CSi), 52.5 (O**C**H_3), 58.8 (C3), 62.5 (C5), 81.5 (C2), 82.9 (C4), 127.7 (ArCH), 129.7 (2 × ArCH), 132.8 (2 × ArC), 135.5 (ArCH), 170.1 (C=O); *m/z* (APCI+ve): 443 ($M+NH_4^+$, 100%), 415 ($M+NH_4^+-N_2$, 75%), 398 ($M+H^+-N_2$, 45%).

4.22. Methyl 2,4-anhydro-3-azido-3-deoxy-D-lyxonate 26

A solution of hydrogen chloride in methanol was prepared by addition of acetyl chloride (0.5 mL) to methanol (10 mL) at 0 °C. This solution was allowed to stir for 15 min and then added dropwise to the silyl protected azide **25** (400 mg, 0.94 mmol). The solution was stirred at room temperature for 18 h after which TLC (1:2, ethyl acetate/hexane) showed the conversion of the starting material (R_f 0.62) into one major product (R_f 0.07). The solution was neutralised with sodium bicarbonate filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (1:4, ethyl acetate/hexane) to give the deprotected *cis*-azido ester **26** as a colourless oil (133 mg, 76%). HRMS *m/z* (CI+): found 205 09375 ($M+NH_4^+$); $C_6H_{13}N_4O_4$ requires 205.09368; $[\alpha]_D^{26} = +10.4$ (*c*, 0.99 in $CHCl_3$); ν_{max} (thin film): 3456 (br, m, OH), 2119 (s, N_3), 1754 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 2.25–2.35 (1H, br, s, OH), 3.84 (3H, s, OMe), 3.94 (1H, s, H5), 3.95 (1H, s, H5′), 4.76–4.86 (2H, m, H3, H4), 5.06 (1H, d, H2, *J* 5.7); δ_C ($CDCl_3$, 100 MHz): 52.7 (O**C**H_3), 58.7 (C3), 61.7 (C5), 81.9 (C2), 82.5 (C4), 169.9 (C=O); *m/z* (APCI+ve): 205 ($M+NH_4^+$, 100%), 177 ($M+NH_4^+-N_2$, 45%), 160 ($M+H^+-N_2$, 10%).

4.23. Methyl 2,4-anhydro-3-azido-5-*O*-*tert*buytldimethylsilyl-3-deoxy-D-lyxonate 3

TBDMS triflate (0.74 mL, 3.2 mmol) was added dropwise to a solution of alcohol **26** (300 mg, 1.6 mmol) in dichloromethane (9.6 mL) and pyridine (0.52 mL, 6.4 mmol) at −20 °C; the reaction mixture was stirred at −20 °C for 20 min, allowed to warm to 0 °C and then for 1.5 h after which time the complete conversion of starting alcohol (R_f 0.38 1:1 ethyl acetate/hexane) to product (R_f 0.91) was observed. The reaction mixture was diluted with dichloromethane (30 mL) and washed with water (15 mL). The aqueous layers were further extracted with dichloromethane (3 × 10 mL), the combined organic layers dried over magnesium sulfate and evaporated under reduced pressure. The product was purified by flash column chromatography (1:2 ethyl acetate/hexane) to yield the *cis*-azido ester **3** as a colourless oil (480 mg, 99%) HRMS *m*/*z* (CI+): found 302.1536 ($M+H^+$); $C_{12}H_{24}N_3O_4Si$ requires 302.1543; $[\alpha]_D^{25} = +33.2$ (*c*, 1.02 in $CHCl_3$); ν_{max} (thin film): 2116 (s, N_3), 1760 (m, C=O); δ_H ($CDCl_3$, 400 MHz): 0.10 (2 × 3H, s, $Si(C\mathbf{H}_3)_2$), 0.91 (9H, s, $(C\mathbf{H}_3)_3CSi$), 3.84 (3H, s, OMe), 3.85–3.89 (1H, dd, H5, *J* 4.7, 11.2), 4.03–4.07 (1H, dd, H5′, *J* 6.4, 11.2), 4.70–4.74 (1H, dd, H3, *J* 5.8, 7.0), 4.79–4.84 (1H, m, H4), 4.93 (1H, d, H2, *J* 5.7); δ_C ($CDCl_3$, 100 MHz): −5.5, −5.2 (2 × $Si(\mathbf{C}H_3)_2$), 18.3 ($Si\mathbf{C}(CH_3)_3$), 25.6, 25.8 (3 × $SiC(\mathbf{C}H_3)_3$), 52.6 ($O\mathbf{C}H_3$), 58.7 (C3), 61.9 (C5), 81.4 (C2), 83.0 (C4), 170.2 (C=O); *m*/*z* (APCI+ve): 319 ($M+NH_4^+$, 100%), 302 ($M+H^+$, 80%), 291 ($M+NH_4^+-N_2$, 63%), 274 ($M+H^+-N_2$, 45%).

4.24. Methyl 2,4-anhydro-5-deoxy-4-*O*-benzoyl-D-lyxonate 27

Bromide **11** (2.0 g, 6.1 mmol) was dissolved in toluene (40 mL), after which tris(trimethylsilyl)silane (4.1 mL, 24.4 mmol) and AIBN (200 mg, 1.22 mmol) were added. The reaction mixture was flushed with nitrogen and stirred at 60 °C. Further additions of AIBN (3 × 200 mg) were made after 30, 60 and 90 min. After 3 h, TLC (dichloromethane) showed the formation of a major product (R_f 0.2). The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (1:8, ethyl acetate/hexane) to give the product **27** as a pale yellow viscous oil (854 mg, 56%). Found: C, 62.19, H, 5.62; $C_{13}H_{14}O_5$ requires: C, 62.39, 5.64; HRMS *m*/*z* (CI+): found: 251.0922 ($M+H^+$); $C_{13}H_{15}O_5$ requires: 251.0920; $[\alpha]_D^{20} = +50.7$ (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 1724 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.47 (3H, d, H5, *J* 6.5), 3.87 (3H, s, OMe), 5.10 (1H, dd, H2, *J* 1.0, 4.5), 5.27 (1H, m, H4), 5.72 (1H, dd, H3, *J* 4.8, 6.5), 7.62 (2H, m, ArH), 7.90 (1H, m, ArH), 8.09–8.12 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 16.0 (C5), 52.6 ($O\mathbf{C}H_3$), 59.9 (C4), 71.3 (C3), 81.0 (C2), 128.6 (ArCH), 128.7 (ArCH), 129.8 (ArCH), 133.7 (ArC), 170.3 (MeO**C**=O), 202.6 (PhO**C**=O); *m*/*z* (APCI+ve): 251 ($M+H^+$, 32%), 147 (100%).

4.25. Methyl 2,4-anhydro-5-deoxy-D-lyxonate 30

Benzoate ester **27** (200 mg, 0.8 mmol) was dissolved in a mixture of THF (4.3 mL) and water (0.6 mL). Sodium hydroxide (1 M, aq, 0.8 mL, 0.8 mmol) was added and the reaction mixture stirred for 18 h after which time TLC (1:1, EtOAc/hexane) showed the complete loss of the starting material to give **29**. The reaction mixture was diluted with methanol (100 mL), after which conc HCl was added (1 mL) and the reaction stirred at room temperature for 18 h at which point TLC (1:1 EtOAc/hexane) showed complete conversion of the intermediate and formation of the title compound **30** (R_f 0.40). The reaction mixture was neutralised ($NaHCO_3$, aq, sat) to pH 5 and concentrated in vacuo. The residue was diluted dichloromethane (50 mL) and washed with NaOAc (sat, aq, 20 mL). The aqueous layer was further extracted with dichloromethane (3 × 20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (1:1, EtOAc/hexane) to yield alcohol **30** as a volatile colourless oil (75 mg, 78%). The product was too volatile for analysis by CHN or HRMS. $[\alpha]_D^{20} = -45.3$ (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 3420 (br, m, OH), 1739 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.45 (3H, d, Me, *J* 6.8), 2.62 (1H, d, OH, *J* 6.1), 3.82 (3H, s, OMe), 4.80 (1H, a-q, H3, *J* 5.7), 4.95 (1H, dd, H2, *J* 0.7, 5.1), 5.02 (1H, a-d quintet, H4, *J* 0.9, 6.5); δ_C ($CDCl_3$, 100 MHz): 15.3 (C5), 52.4 ($O\mathbf{C}H_3$), 69.9 (C3), 82.5 (C4), 84.8 (C2), 171.3 (C=O); *m*/*z* (APCI+ve): 164 ($M+NH_4^+$, 100%).

4.26. Methyl 2,4-anhydro-5-deoxy-3-*O*-trifluoromethanesulphonyl-D-lyxonate 32

Alcohol **30** (50 mg, 0.34 mmol) was dissolved in dichloromethane (6 mL) and pyridine (0.083 mL, 1.02 mmol) added. The reaction mixture was cooled to −30 °C and triflic anhydride (0.092 mL, 0.55 mmol) added dropwise. The reaction was stirred for 3.5 h at −30 to −10 °C after which time TLC (1:4, ethyl acetate/hexane) showed the formation of one major product (R_f 0.55). The reaction mixture was diluted dichloromethane (30 mL) and washed with 2 M HCl (10 mL). The aqueous layer was further extracted with dichloromethane (3 × 10 mL) and the combined organic layers washed with brine (30 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (1:3, ethyl acetate/hexane) to give the triflate **32** as a yellow oil (90 mg, 94%). Found: C, 30.26, H, 3.30; $C_7H_9F_3SO_6$ requires: C, 30.22, H, 3.26; $[\alpha]_D^{22} = +22.6$ (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 1750 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.56 (3H, d, H5, *J* 6.8), 3.87 (3H, s, OMe), 5.16 (1H, dd, H2, *J* 1.2, 4.6), 5.19 (1H, a-d quintet, H4, *J* 1.3, 6.2), 5.63 (1H, a-t, H3, *J* 5.3); δ_C ($CDCl_3$, 100 MHz): 16.0 (C5), 52.7 ($O\mathbf{C}H_3$), 60.3 (C3), 80.4 (C4), 80.5 (C2), 168.3 (C=O); *m*/*z* (APCI+ve): 279 ($M+H^+$, 8%), 104 (100%).

4.27. Methyl 2,4-anhydro-3-azido-5-deoxy-D-arabinonate 6

Sodium azide (43 mg, 0.66 mmol) was added to a solution of triflate **32** (122 mg, 0.44 mmol) in DMF (5 mL). The reaction mixture was stirred at room temperature for 3 h after which time TLC (1:1, ethyl acetate/hexane) showed the complete conversion of triflate (R_f 1.0) into one major product (R_f 0.6). The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (50 mL) and washed with brine (30 mL). The aqueous layer was further extracted with ethyl acetate

(3×10 mL) and the combined organic layers dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography to give azide **6** as a light yellow oil (69 mg, 92%). HRMS (CI+): found 189.0994 ($M+NH_4^+$); $C_6H_{13}N_4O_3$ requires 189.0988; $[\alpha]_D^{25} = +123.9$ (c, 0.36 in $CHCl_3$); ν_{max} (thin film): 2114 (s, N_3) 1736 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.51 (3H, d, H5, J 4.7), 3.89 (3H, s, OMe), 4.44 (1H, a-t, H3, J 6.3), 4.88 (1H, a-quintet, H4, J 6.0), 5.16 (1H, d, H2, J 7.9); δ_C ($CDCl_3$, 100 MHz): 21.2 (C5), 52.4 (OCH_3), 61.6 (C3), 78.6 (C2), 84.3 (C4), 169.7 (C=O); m/z (APCI+ve): 172 ($M+H^+$, 11%), 189 ($M+NH_4^+$, 100%).

References

1. Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A.; Matsumoto, T. *J. Antibiot.* **1984**, *37*, 1324–1332.
2. (a) Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M.; Omura, S. *Chem. Pharm. Bull. Tokyo* **1986**, *34*, 3102–3110; (b) Bach, T.; Schroder, J. *Liebigs Ann. Recl.* **1997**, 2265–2267.
3. Loh, J.; Carlson, R. W.; York, W. S.; Stacey, G. *Proc. Natl. Acad. Sci.* **2002**, *99*, 14446–14451.
4. (a) Kobayashi, H.; Graven, Y. N.; Broughton, W. J.; Perret, X. *Molecul. Microbiol.* **2004**, *51*, 335–347; (b) Lyon, G. J.; Muir, T. W. *Chem. Biol.* **2003**, *10*, 1007–1010.
5. 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.
6. 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.
7. Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.
8. Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
9. Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913–941.
10. (a) Raguse, T. L.; Lai, J. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 5592–5593; (b) Lai, J. R.; Gellman, S. H. *Protein Sci.* **2003**, *12*, 560–566; (c) Raguse, T. L.; Lai, J. R.; Gellman, S. H. *Helv. Chim. Acta* **2002**, *85*, 4154–4164; (d) Bruckner, A. M.; Chakraborty, P.; Gellman, S. H.; Diederichsen, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4395–4399; (e) Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 9035–9037; (f) Rueping, M.; Mahajan, Y. R.; Jaun, B.; Seebach, D. *Chem. Eur. J.* **2004**, *10*, 1607–1615; (g) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1595–1597; (h) Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 505–510.
11. (a) Lelais, G.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4152–4168; (b) Daura, X.; Bakowies, D.; Seebach, D.; Fleischhauer, J.; van Gunsteren, W. F.; Kruger, P. *European. Biophys. J. Biophys. Lett.* **2003**, *32*, 661–670; (c) Rossi, F.; Lelais, G.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 2653–2661; (d) Gessier, F.; Noti, C.; Rueping, M.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 1862–1870.
12. Beke, T.; Csizmadia, I. G.; Perczel, A. *J. Computat. Chem.* **2004**, *25*, 285–307.
13. (a) Arvidsson, P. I.; Frackenpohl, J.; Ryder, N. S.; Liechty, B.; Petersen, F.; Zimmermann, H.; Camenisch, G. P.; Woessner, R.; Seebach, D. *Chem. Bio. Chem.* **2001**, *2*, 771–773; (b) Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200–12201; (c) Porter, E. A.; Wang, X. F.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565–566.
14. (a) Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Gross, G.; Kretz, O.; Woessner, R.; Seebach, D. *Chem. Bio. Chem.* **2003**, *4*, 1345–1347; (b) Lai, J. R.; Huck, B. R.; Weisblum, B.; Gellman, S. H. *Biochemistry* **2002**, *41*, 12835–12842; (c) Porter, E. A.; Wang, X. F.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565–565; (d) Gelman, M. A.; Weisblum, B.; Lynn, D. M.; Gellman, S. H. *Org. Lett.* **2004**, *6*, 557–560.
15. Epand, R. F.; Raguse, T. L.; Gellman, S. H.; Epand R. M. *Biophys. J.* **2004**, *86*, 204A–205A.
16. Gelman, M. A.; Richter, S.; Cao, H.; Umezawa, N.; Gellman, S. H.; Rana, T. M. *Org. Lett.* **2003**, *5*, 3563–3565.
17. Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774–1783.
18. (a) Seebach, D.; Rueping, M.; Arvidsson, P. I.; Kimmerlin, T.; Micucu, P.; Noti, C.; Langeneggaer, D.; Hoyer, D. *Helv. Chim. Acta* **2001**, *84*, 3503–3510; (b) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460–2468; (c) Gademann, K.; Ernst, M.; Seebach, D.; Hoyer, D. *Helv. Chim. Acta* **2000**, *83*, 16–33; (d) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223–1226.
19. Gademann, K.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 2924–2937.
20. (a) Miyata, O.; Namba, M.; Ueda, M.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1274–1276; (b) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J. C.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong, J. D.; Sun, Y. K.; Mathre, D. J.; Grabowski, E. J. J.; Tillyer, R. *J. Am. Chem. Soc.* **2004**, *126*, 3048–3049; (c) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634–1645; (d) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901–903; (e) Davies, S. G.; Hermann, G. J.; Sweet, M. J.; Smith, A. D. *Chem. Commun.* **2004**, 1128–1129.
21. (a) Li, K. L.; Cheng, X. H.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959–964; (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587–590; (c) Huck, J.; Roumestant, M. L.; Martinez, J. *J. Pept. Res.* **2003**, *62*, 233–237.
22. (a) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467; (b) Bailey, S.; Davies, S. G.; Smith, A. D.; Withey, J. M. *Chem. Commun.* **2002**, 2910–2911; (c) Forro, E.; Fulup, F. *Tetrahedron: Asymmetry* **2004**, *15*, 573–575.
23. Langer, O.; Kahlig, H.; Zierler-Gould, K.; Bats, J. W.; Mulzer, J. *J. Org. Chem.* **2002**, *67*, 6878–6883.
24. Izquierdo, S.; Martin-Vila, M.; Moglioni, A. G.; Branchadell, V.; Ortuno, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2403–2405.
25. Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884–7886.
26. (a) Locardi, E.; Stöckle, M.; Gruner, S.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189–8196; (b) Schweizer, F. *Angew. Chem.* **2001**, *41*, 230–253; (c) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514.
27. 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.

28. (a) Chakraborty, T. K.; Jayaprakash, S.; Ghosh, S. *Comb. Chem. High Throughput Scr.* **2002**, *5*, 373–387; (b) Edwards, A. A.; Ichihara, O.; Murfin, S.; Wilkes, R.; Watkin, D. J.; Fleet, G. W. J. *J. Combinatorial Chem.* **2004**, *6*, 230–238.
29. (a) Watterson, M. P.; Pickering, L.; Smith, M. D.; Hudson, S. H.; Marsh, P. R.; Mordaunt, J. E.; Watkin, D. J.; Newman, C. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1855–1859; (b) Taillefumier, C.; Thielges, S.; Chapleur, Y. *Tetrahedron* **2004**, *60*, 2213–2224.
30. van Well, R. M.; Meijer, M. E. A.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A.; Overhand, M. *Tetrahedron* **2003**, *59*, 2423–2434.
31. Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sharma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441–6457.
32. 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.
33. (a) 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; (b) Smith, M. D.; Claridge, T. D. W.; Sansom, M. P.; Fleet, G. W. J. *Org. Biomol. Chem.* **2003**, *1*, 3647–3655; (c) Chakraborty, T. K.; Srinivasu, P.; Madhavendra, S. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3573–3577; (d) 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.
34. Watterson, M. P.; Edwards, A. A.; Leach, J. A.; Smith, M. D.; Ichihara, O.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5853–5856.
35. Grotenbreg, G. M.; Spalburg, E.; de Neeling, A. J.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Overhand, M. *Bioorg. Med. Chem.* **2003**, *11*, 2835–2841.
36. Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041–2042.
37. 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.
38. (a) Witty, D. R.; Fleet, G. W. J.; Vogt, K.; Wilson, F. X.; Wang, Y.; Storer, R.; Myers, P. L.; Wallis, C. J. *Tetrahedron Lett.* **1990**, *31*, 4787–4790; (b) Elliott, R. P.; Fleet, G. W. J.; Vogt, K.; Wilson, F. X.; Wang, Y.; Witty, D. R.; Storer, R.; Myers, P. L.; Wallis, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 715–718.
39. Sun, R. C.; Okabe, M. *Org. Synth.* **1993**, *72*, 48–56.
40. Wang, Y.; Fleet, G. W. J.; Storer, R.; Myers, P. L.; Wallis, C. J.; Doherty, O.; Watkin, D. J.; Vogt, K.; Witty, D. R.; Wilson, F. X.; Peach, J. M. *Tetrahedron: Asymmetry* **1990**, *1*, 527–531.
41. Han, S.-Y.; Joullie, M. M.; Fokin, V. V.; Petasis, N. P. *Tetrahedron: Asymmetry* **1994**, *5*(12), 2535–2562.
42. DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*(5), 669–672.
43. (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.
44. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
45. (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641–3642; (b) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1989**, *54*, 2492–2494; (c) Lesage, M.; Chatgilialoglu, C.; Griller, D. *Tetrahedron Lett.* **1989**, *30*, 2733–2734.
46. Johnson, S. W.; Jenkinson (née Barker), S. F.; Angus, D.; Taillefumier, C.; Jones, J. H.; Fleet. G. W. J. *Tetrahedron: Asymmetry* **2004**, *15*, following paper. doi:10.1016/j.tetasy.2004.07.032.
47. Wang, Y.; Fleet, G. W. J.; Wilson, F. X.; Storer, R.; Myers, P. L.; Wallis, C. J.; Doherty, O.; Watkin, D. J.; Vogt, K.; Witty, D. R.; Peach, J. M. *Tetrahedron Lett.* **1991**, *32*(13), 1675–1679.