Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4113–4125

TETRAHEDRON: *ASYMMETRY*

Two epimerisations in the formation of oxetanes from L-rhamnose: towards oxetane-containing peptidomimetics

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Received 15 August 2000; accepted 11 September 2000

Abstract

The methyl group in (*R*)-3,5-*O*-benzylidene-L-*rhamnono*-1,4-lactone **2**, prepared from L-rhamnose **1** in 41% yield without need for chromatography, is axial and provides a good example of Mills' rule that the 'O-inside' conformations are, in general, more stable than alternative 'H-inside' conformations. The lactone **2** may be converted in two steps in an overall 57% yield to the *rhamnono*-oxetane **3**, which should be useful in generating oxetane dipeptide isosteres and oxetane β-amino acids and in determining the value of the oxetane ring in inducing secondary structure in small peptidomimetics. Methyl 2,4-anhydro-(*S*)-3,5-*O*-benzylidene-L-rhamnonate **11**, in which both the phenyl and methyl groups are equatorial, is slightly more thermodynamically stable than **3**, providing a rare exception to Mills' rule. X-ray crystal structures of **2** and **11** are reported. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Unnatural biopolymers[1] that adopt well-defined conformations might be designed to possess biological activities similar to those of proteins and peptides (foldamers).[2] For example, β-amino acids provide well-defined secondary structural features in sequences far shorter than those of proteinogenic amino acids;[3] a hetero-oligomer of some cyclopentane β-amino acids mimics natural antibiotics.[4] There are many potential clinical applications of such materials.[5]

Carbohydrate scaffolds offer a large family of monomers with the ability to tune predisposition towards specific secondary structures. Pyranose sugar amino acids have been shown to exert predictable conformational effects in peptidic systems due to the rigid chain conformations imposed in a glucose framework by the all-equatorial substituents; when such systems were incorporated into cyclic hexapeptide analogues of somatostatin, a γ-amino acid served as a

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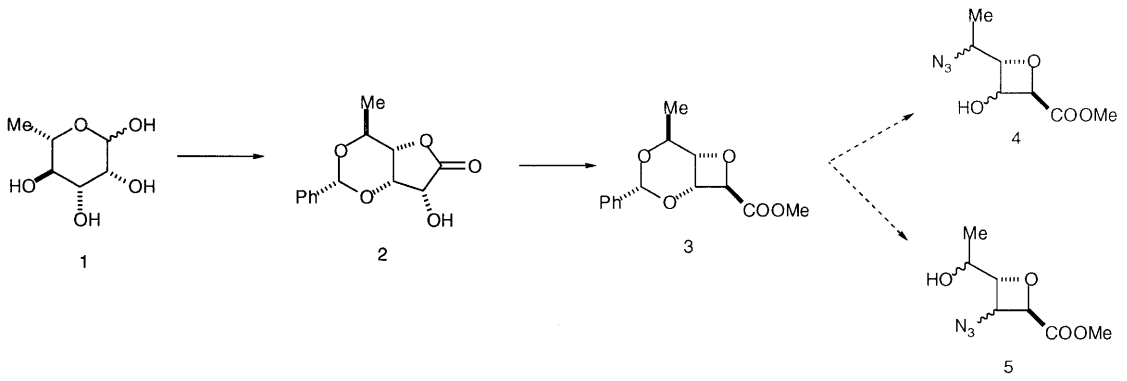
PII: S0957-4166(00)00360-8

β-turn mimetic while a β-amino acid induced a γ-turn.[6] A pyranose amino acid has been incorporated as a dipeptide isostere in the design of a peptide which is a farnesyl transferase inhibitor.[7] The tetrahydrofuran (THF) ring is less flexible than many pyranoses. 5-Azidomethyl-tetrahydrofuran-carboxylic acid scaffolds (building blocks for δ-oligopeptides) provide a set of dipeptide isosteres which are predisposed towards different secondary structures, depending on the stereochemistry of the substituents around the THF ring;[8] different diastereomers form β-turn[9] and left-handed helical[10] solution structures. A THF sugar amino acid was incorporated into Leu-enkephalin as a Gly–Gly substitute to provide opioids equipotent with the natural peptide; CD studies indicated that such carbopeptoids may have a β-turn-like structure.[11] THF amino acids have been incorporated into a functional cation channel with a biomimetic channel entrance and exit; four THF amino acids continue the gramicidin β-helix.[12]

As yet, there are no reports of the incorporation of oxetane scaffolds into carbopeptides. For such studies, short and efficient routes to a range of oxetane amino acids are necessary. This paper describes the conversion of L-rhamnose **1** into a crystalline benzylidene-protected lactone **2** on a multigram scale with no need for column separation (Scheme 1); the lactone **2** is transformed in two steps to the protected oxetane **3** in an overall yield of 57%, even though the ring closure takes place with overall retention of configuration at C-2 of the lactone. The new stereogenic centre on **2** results in the methyl group being axial and provides a good example of Mills' rule[13] that the 'O-inside' conformations are in general more stable than alternative 'H-inside' conformations. The protected oxetane **3** should act as a convenient divergent intermediate for the formation of the diastereomeric dipeptide isosteres **4** and of the β-azido acids **5**. The X-ray crystal structures of the benzylidene lactone **2** and of the benzylidene oxetane **11** clearly show the C-6 methyl group in axial and equatorial environments, respectively.



Scheme 1.

2. Synthesis and discussion

2.1. Formation of the benzylidene acetal **2**

Oxidation of L-rhamnose **1** with bromine water gives a mixture of 1,4- and 1,5-*rhamnono*-lactones;[14] treatment of the crude mixture of lactones, still substantially contaminated with inorganic salts, with benzaldehyde allowed the isolation of the highly crystalline benzylidene

lactone **2** in an overall yield of 41% from L-rhamnose **1** on a multigram scale. The structure of **2** was firmly established by X-ray crystallographic analysis (Fig. 1). There are two possible epimeric benzylidene lactones in which the phenyl group is equatorial in the six-membered acetal ring. The isolated *R*-**2** product has the Me group axial, and so it might be expected to be disfavoured relative to *S*-*epi*-**2** in which both the phenyl and methyl groups are equatorial.

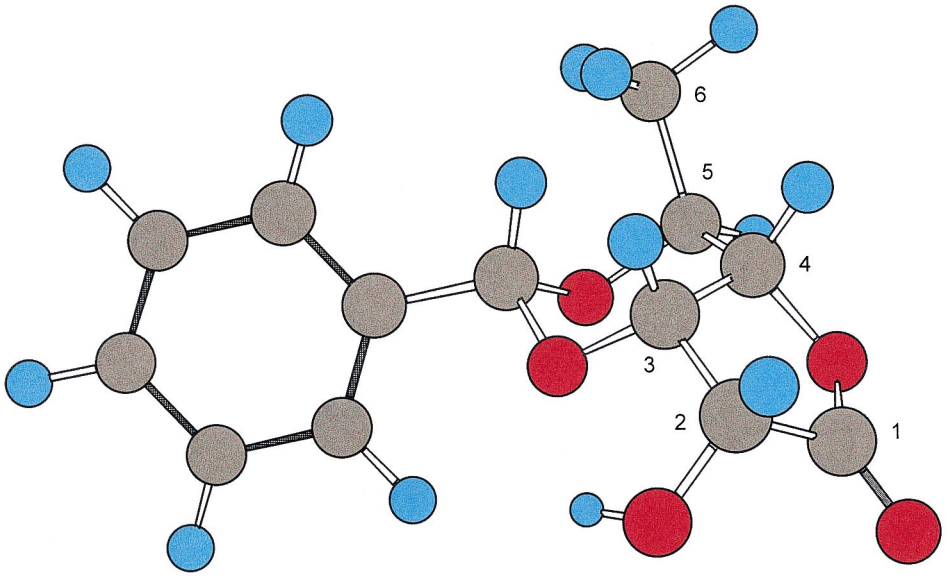
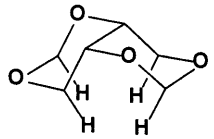
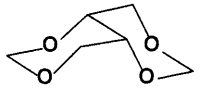


Figure 1. X-ray crystal structure of (*R*)-3,5-*O*-benzylidene-L-*rhamnono*-1,4-lactone **2** (grey = C, red = O, blue = H)

The conformation about the C-4 to C-5 bond is very different for the two diastereoisomers **2** and *S*-*epi*-**2**, and is shown in the Newman projections (Fig. 2). In the case of **2**, both the H-4 and H-5 protons are located in equatorial positions and the observed vicinal coupling constant $J_{4,5} = 1$ Hz is small. If *S*-*epi*-**2** had been formed a much larger *trans*-diaxial coupling would have been expected. The configuration of the benzylic carbon atom in benzylidene-protected sugar derivatives was investigated as long ago as 1954.[15] A review by Mills[13] in 1955 discussed the conformation of bicyclic diacetals with *cis*-ring junctions (as in this case) in terms not only of the axial and equatorial positions of residues, but also in consideration of the possibilities of 'H-inside' and 'O-inside' conformations; Mills predicted that in general the 'O-inside' conformation is more stable than the 'H-inside' conformation, but that the situation may be clouded somewhat by the nature of other substituents on the ring.



"H-inside"



"O-inside"

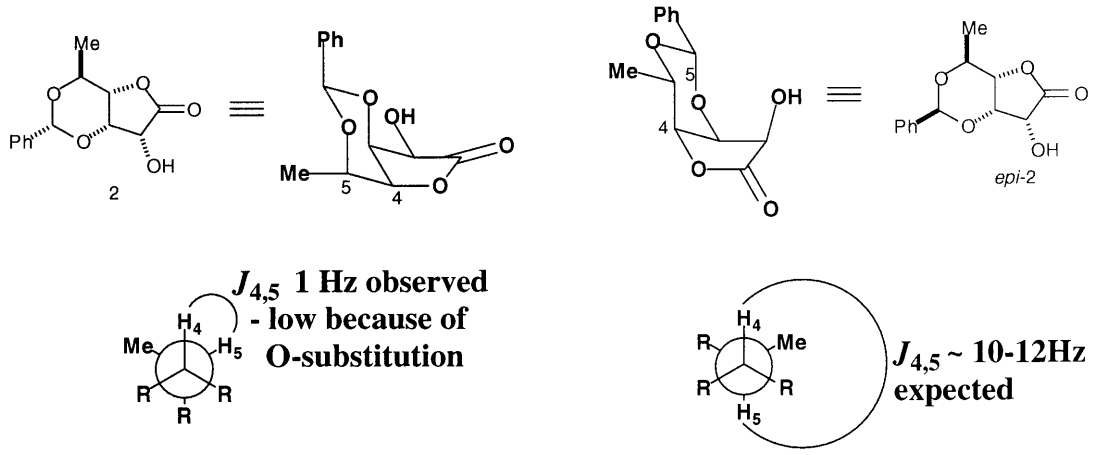
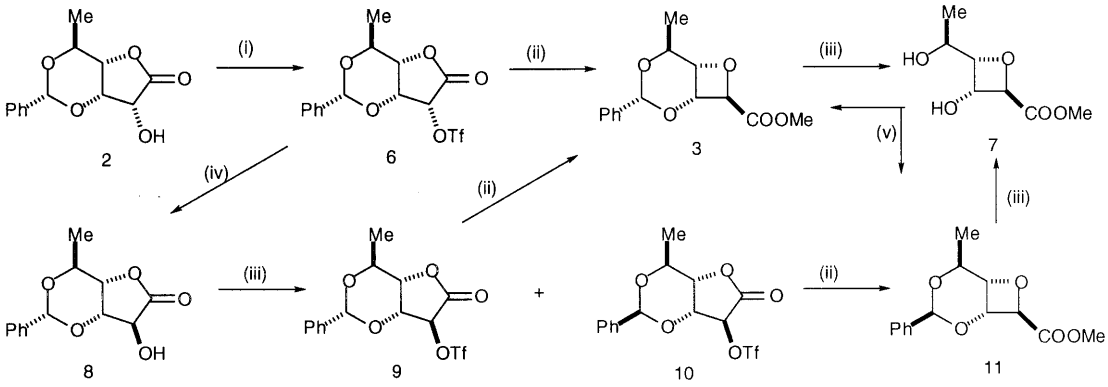


Figure 2.

Further work by Angyal,[16] Foster and co-workers,[17] and Buchanan[18] extended and supported these general conclusions. The formation of **2** with an axial methyl group in preference to an alternative equatorial substituent in *S-epi*-**2** is in accordance with Mills' analysis.

2.2. Formation of the oxetane ring *3*

The synthesis of the oxetane **3** required introduction of a good leaving group at C-2 of the lactone **2**.[19] Esterification of the alcohol **2** with trifluoromethanesulfonic (triflic) anhydride in the presence of pyridine in THF afforded the stable triflate **6** in 70% yield (Scheme 2). Treatment of the triflate **6** with potassium carbonate in methanol allowed the formation of the oxetane **3** in a yield of 77% on a 1 g scale. This procedure gives efficient access to the benzylidene derivative **3** in three steps from rhamnose.



Scheme 2. (i) $(CF_3SO_2)_2O$, pyridine, THF; (ii) K_2CO_3, MeOH; (iii) HCl, MeOH; (iv) CF_3COOCs, MeCOEt; (v) $PhCH(OMe)_2$, TsOH, DMF

Alternatively, reaction of the *rhamnono*-triflate **6** with caesium trifluoroacetate in butanone[20] gave the epimeric L-*glucono*-lactone **8** in 90% yield. Esterification of **8** with triflic anhydride gave

the corresponding (*R*)-benzylidene triflate **9** in good yield, provided the work-up was conducted rapidly; however, it was clear that the triflate **9** was unstable to silica chromatography, during which it decomposed and, to some extent, unexpectedly formed the epimeric (*S*)-benzylidene triflate **10**. The combined yield and ratio of the two triflates **9** and **10** depended on the work-up procedures (Fig. 3).

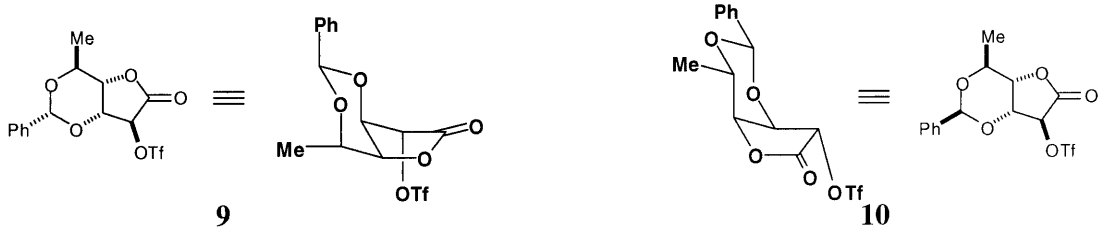


Figure 3.

During the triflation reaction of the *glucono*-lactone **8**, an NMR of the crude product showed that only the expected triflate **9** was present. Various ratios of the two triflates were found depending on the time spent on the column, and in all cases purification by flash chromatography reduced the yield considerably. The ^{1}H NMR spectrum of **9** showed that $J_{2,3}=1.4$ Hz and $J_{4,5}=2.3$ Hz. This is clearly consistent with none of the hydrogens being *trans*-diaxially arranged in the (*R*)-epimer **9**; in contrast, the spectrum of **10** gave $J_{2,3}=9.6$ Hz and $J_{4,5}=10.1$ Hz, consistent with these sets of hydrogens being *trans*-diaxially arranged. Unsuccessful attempts were made to equilibrate the two acetal epimers in acidic solution (acidified with TFA and/or silica), and by dry loading the compound onto silica.

When the crude triflate **9** was treated with potassium carbonate in methanol, a mixture of the (*R*)-benzylidene oxetane **3** (54%) and the (*S*)-benzylidene oxetane **11** (9%) was obtained. Reaction of the relatively stable pure (*S*)-benzylidene triflate **10** under the same conditions gave the pure (*S*)-benzylidene oxetane **11** in 75% yield without any of the epimeric oxetane **3** being formed. The structure of the (*S*)-epimer **11** was firmly established by X-ray crystallographic analysis (Fig. 4).

Methanolysis of the benzylidene acetal **3** with a solution of hydrogen chloride in methanol gave the diol **7** in 54% yield. Reprotection was achieved by treatment of **7** with benzaldehyde dimethyl acetal[21] in DMF in the presence of tosic acid; analysis of the reaction mixture after 3 and 6 days by ^{1}H NMR spectroscopy revealed in each case a 1:4 ratio for the PhC*H* singlet at δ 5.72 for (*R*)-**3** relative to the PhC*H* singlet at δ 6.16 for (*S*)-**11**. This evidence suggests that the (*S*)-epimer **11** is more stable in the 'H-inside' conformation than the 'O-inside' (*R*)-epimer **3**. This may be because, with an oxetane ring rather than a pyran ring attached to the 1,3-dioxane, the H–H steric interactions in the 'H-inside' conformation are much smaller (Fig. 5); as a result, the axial versus equatorial considerations of the substituents play a much more dominant role in deciding the overall stability. If this is the case, it is a rare example of change in the ring *cis*-fused to the benzylidene ring causing a change in the conformational/configurational preference of the molecule.[16]

The formation of the oxetane ring in **3** by an intramolecular S_N2 reaction from the *rhamnono*-lactone triflate **6** (with overall retention of configuration at C-2) is considerably more efficient overall than from the epimeric triflate **9** (with inversion of configuration at C-2). Oxetane-2-carboxylates are formed in high yield from carbohydrate lactone triflates *provided*

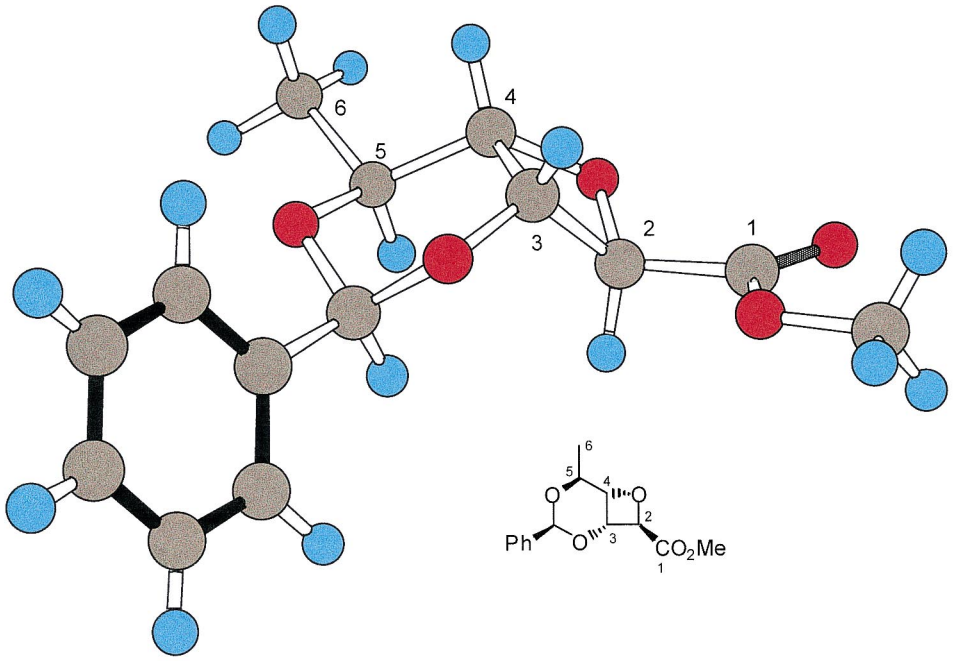


Figure 4. X-ray crystal structure of methyl 2,4-anhydro-(*S*)-3,5-*O*-benzylidene-L-rhamnonate **11** (grey = C, red = O, blue = H)

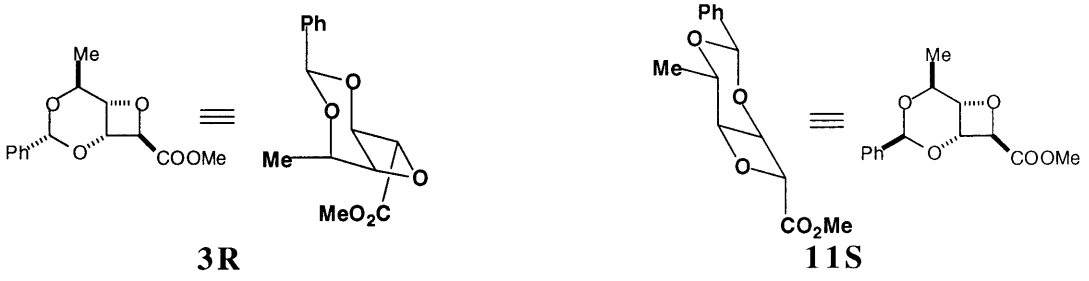
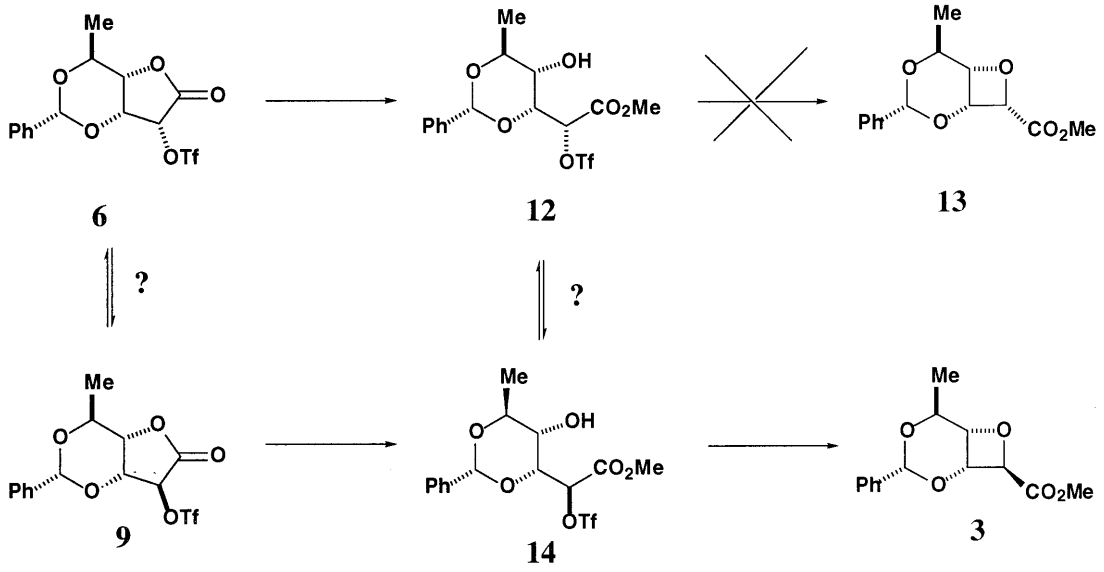


Figure 5.

that the oxygen substituent at C-3 is *trans* to the carboxylate at C-2.[22] It may be that the difficulty in S_N2 reactions caused by a β-oxygen substituent means the late transition state for the closure reflects the crowding in the incipient product; cyclisations which lack the neighbouring oxygen may not show such strong preferences for 2,3-*trans*-oxetanes.[23] For the efficient formation of **3** from **6** (Scheme 3), ring opening of the lactone **6** by methanol would give the open chain triflate **12**, which does not close to **13**; there was no evidence for the formation of any of the all *cis*-substituted **13** in any of the experimental conditions reported in this paper. Subsequent epimerisation of **12** to **14** would then allow ring closure to the 2,3-*trans*-oxetane **3**. Alternatively it is just possible that epimerisation of **6** to **9** precedes ring opening, giving **14** directly.



Scheme 3.

3. Summary

This paper reports the formation of an easily crystallised benzylidene L-*rhamnono*-lactone **2** which may be prepared from L-rhamnose **1** without any column chromatography; formation of **2** in which the C-6 methyl group is axial, rather than the alternative epimer in which it would be equatorial, provides a good example of Mills' rule[13] that the 'O-inside' conformations are in general more stable than alternative 'H-inside' conformations. The lactone **2** may be converted in two steps in an overall 57% yield to the *rhamnono*-oxetane **3** in which the formation of the oxetane occurs with overall retention of configuration at C-2 of the sugar moiety. The benzylidene oxetane **11** in which both the phenyl and methyl groups are equatorial is slightly more thermodynamically stable than **3**, providing a rare exception to Mills' rule. The oxetane **3** should be useful in generating oxetane dipeptide isosteres and oxetane β-amino acids in order to determine the value of the oxetane ring in inducing secondary structure in small peptidomimetics.

4. Experimental

Dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over a dried 4 Å molecular sieve. THF and DMF were purchased dry from the Aldrich Chemical Company in Sure-Seal™ bottles capped with Oxford-Caps™. Hexane refers to the fraction of petroleum ether which boils in the range 60–80°C. All other solvents were used as supplied (Analytical or HPLC grade), without further purification. Reactions performed under an atmosphere of nitrogen were maintained by an inflated balloon. A buffer of pH 7 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 further purification. Thin layer chromatography (TLC) was performed on aluminium backed sheets coated with 60 F_{254} silica. Sheets were

developed using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was performed using C60 40/60 silica. Melting points were recorded on a Kofler hot block. NMR spectra were recorded on either a Bruker DPX 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in the deuteriated solvent stated. All 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 spectrophotometer using thin films on NaCl plates. High resolution mass spectra (HRMS m/z) were recorded on a micromass Autospec 500 OAT spectrometer using the technique of chemical ionisation (NH_3, CI). Low resolution mass spectra were recorded on a VG PLATFORM (APCI, positive or negative as stated). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml. The wavelength at which the rotations were measured corresponds to the sodium D line. Elemental analyses were performed either by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford, or by Elemental Microanalysis Limited, Okehampton, Devon. Except where otherwise stated, crystalline compounds were obtained by concentration or complete evaporation of eluants obtained from flash chromatography.

4.1. (R)-3,5-O-*Benzylidene*-L-rhamnono-1,4-*lactone* **2**

Barium carbonate (86.6 g, 440 mmol) was added to a stirred solution of L-rhamnose monohydrate **1** (40.2 g, 220 mmol) in water (300 ml) at 0°C. Bromine (17 ml, 330 mmol) was added to the solution (3×5.67 ml portions at 15 min intervals). The reaction mixture was then stirred at 0°C for 1 h, and then allowed to warm to room temperature. After 15 h at room temperature, TLC (ethyl acetate:methanol, 9:1) revealed that the starting material (R_F 0.21) had been completely consumed, and replaced by a major product (R_F 0.34) and a minor product (R_F 0.48). The reaction mixture was then filtered through Celite, and the solid was washed with water. Nitrogen was bubbled through the filtrate until the solution was decolourised, and the solvent was removed. The solid was extracted with refluxing acetone (12×250 ml), and the acetone was then removed to give a white solid (18.2 g), still containing inorganic impurities, which was used without further purification. This crude lactone mixture (11.5 g) in benzaldehyde (130 ml) was treated with concentrated hydrochloric acid (40 ml); the reaction mixture was stirred at room temperature for 2.4 h, and TLC (ethyl acetate:hexane, 2:1) revealed the formation of a major product (R_F 0.23). Approximately half the solvent was then removed, and ether added until the product crystallised out; the solid was collected by filtration and washed with ether; concentration of the ether washings gave the crystalline product (12.3 g). The solvent was then removed from the concentrated washings, and the residue purified by flash chromatography (ethyl acetate:hexane, 2:1) to give further product (1.90 g). The crystalline material was combined to give (*R*)-3,5-*O*-benzylidene-L-*rhamnono*-1,4-lactone **2** as a white crystalline solid, (14.3 g, 41%), m.p. 175–177°C; $[\alpha]_D^{22}$ –48.7 (c 0.99 in MeCN); ν_{max} (NaCl) 3353 cm^{-1} (O–H), 1775 cm^{-1} (C=O); δ_H (CD_3CN, 200 MHz) 1.49 (d, 3H, H-6, $J_{5,6}=7.2$ Hz), 3.85 (d, 1H, –OH, $J_{2,OH}=9.2$ Hz), 4.13 (dd, 1H, H-4, $J_{3,4}=2.2$ Hz, $J_{4,5}=1.0$ Hz), 4.47 (q, 1H, H-5, $J_{5,6}=7.2$ Hz), 4.56 (dd, 1H, H-2, $J_{2,OH}=9.1$ Hz, $J_{2,3}=4.1$ Hz), 4.79 (dd, 1H, H-3, $J_{2,3}=4.0$ Hz, $J_{3,4}=2.1$ Hz), 5.89 (s, 1H, PhC*H*), 7.37–7.44 (m, 5H, Ph); δ_C (CD_3CN, 50.3 MHz) 15.2 (C-6), 70.5 (C-5), 72.5 (C-2), 72.6 (C-3), 73.6 (C-4), 92.4 (Ph*C*H), 127.3, 129.1, 129.9 (Ph), 139.0 (C_{ipso}), 176.2 (C-1). Found: C, 62.13; H, 5.68; $C_{13}H_{14}O_5$ requires: C, 62.39; H, 5.64%.

4.2. (R)-3,5-O-Benzylidene-2-O-trifluoromethanesulfonyl-L-rhamnono-1,4-lactone **6**

Triflic anhydride (17 ml, 0.10 mol) was added dropwise with rapid stirring under an atmosphere of nitrogen to a solution of the benzylidene lactone **2** (14.9 g, 59.5 mmol) and pyridine (22.6 ml, 0.28 mol) in THF (200 ml) at −78°C. After 20 min, a white precipitate started to form, and the reaction mixture was allowed to warm to 0°C for ca. 2 h. When no starting material remained (TLC, ethyl acetate:hexane, 2:1) the mixture was diluted with dichloromethane (300 ml), washed with 0.1 M hydrochloric acid (50 ml), water (70 ml), dried ($MgSO_4$) and reduced to dryness. The solvent was removed and the residue was purified by flash chromatography (ethyl acetate:hexane, 1:2) to give the triflate **6** as a white solid (15.9 g, 70%), m.p. 139–140°C; $[\alpha]_D^{22}$ −63.9 (*c* 0.98 in MeCN); ν_{max} (NaCl) 1795.8 cm^{-1} (C=O); δ_H (CD_3CN, 200 MHz) 1.52 (d, 3H, H-6, $J_{5,6}=7.4$ Hz), 4.35 (dd, 1H, H-4, $J_{3,4}=2.1$ Hz, $J_{4,5}=0.9$ Hz), 4.58 (q, 1H, H-5, $J_{5,6}=7.4$ Hz), 5.21 (dd, 1H, H-3, $J_{2,3}=3.8$ Hz, $J_{3,4}=1.6$ Hz), 5.83 (d, 1H, H-2, $J_{2,3}=4.2$ Hz), 5.94 (s, 1H, C*H*Ph), 7.41 (m, 5H, Ph); δ_C (CD_3CN, 50.3 MHz) 14.8 (C-6), 70.3 (C-5), 71.4 (C-3), 74.1 (C-4), 81.5 (C-2), 92.4 (Ph*C*H), 127.1, 129.3, 130.2 (Ph), 138.3 (C_{ipso}), 169.0 (C-1). Found: C, 43.85; H, 3.69; $C_{14}H_{13}F_3O_7S$ requires: C, 43.98; H, 3.43%.

4.3. Methyl 2,4-anhydro-(R)-3,5-O-benzylidene-L-rhamnonate **3**

The triflate **6** (1.77 g, 4.62 mmol) in methanol (35 ml, HPLC grade) was cooled to −78°C and potassium carbonate (702 mg, 5.1 mmol) was added. The reaction mixture was stirred for 10 min at −78°C, after which the −78°C bath was substituted for a −30°C bath. The temperature was then allowed to warm up to −10°C, which took 20 min (TLC in ethyl acetate:hexane, 1:1 showed that both the starting material and the product had R_F 0.48). The reaction mixture was then filtered through a plug of silica gel; the silica was rinsed with ethyl acetate and the solvent was removed to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:2) to give the benzylidene oxetane **3** as a white solid (0.94 g, 77%), m.p. 115–116°C; $[\alpha]_D^{23}$ +3.0 (*c* 1.01 in $CHCl_3$); ν_{max} (NaCl) 1764 cm^{-1} (C=O); δ_H ($CDCl_3$, 200 MHz) 1.38 (d, 3H, H-6, $J_{5,6}=7.0$ Hz), 3.83 (s, 3H, CO_2Me), 4.43 (dq, 1H, H-5, $J_{4,5}=2.1$ Hz, $J_{5,6}=7.1$ Hz), 4.69 (ddd, 1H, H-4, $J_{2,4}=1.0$ Hz, $J_{3,4}=4.9$ Hz, $J_{4,5}=2.3$ Hz), 4.93 (dd, 1H, H-3, $J_{2,3}=2.4$ Hz, $J_{3,4}=5.0$ Hz), 5.08 (dd, 1H, H-2, $J_{2,3}=2.5$ Hz, $J_{2,4}=0.9$ Hz), 5.72 (s, 1H, PhC*H*), 7.36–7.57 (m, 5H, Ph); δ_C ($CDCl_3$, 50.3 MHz) 16.2 (C-6), 52.7 (CO_2CH_3), 70.8 (C-5), 72.1 (C-3), 79.4 (C-4), 84.1 (C-2), 92.3 (Ph*C*H), 126.3, 128.6, 129.2 (Ph), 138.3 (C_{ipso}), 170.4 (C-1). Found: C, 63.68; H, 6.07; $C_{14}H_{16}O_5$ requires: C, 63.63; H, 6.10%.

This procedure is the most efficient for the formation of **3**; other experiments in which the oxetane **3** is formed are described below.

4.4. (R)-3,5-O-Benzylidene-6-deoxy-L-glucono-1,4-lactone **8**

Caesium trifluoroacetate (11.1 g, 45.5 mmol) was added to a solution of the *rhamnono*-triflate **6** (7.20 g, 18.8 mmol) in butanone (100 ml); the reaction mixture was heated for 2 h at 60°C when TLC (ethyl acetate:hexane, 1:1) indicated that the starting material (R_F 0.59) had been replaced by a major product (R_F 0.48). The solvent was removed, and the residue purified by flash chromatography (ethyl acetate:hexane, 1:1) to give L-*glucono*-1,4-lactone **8** (4.27 g, 90%) as a white crystalline solid; m.p. 145–148°C; $[\alpha]_D^{22}$ −84.1 (*c* 1.15 in MeCN); ν_{max} (NaCl) 3259.1 cm^{-1} (O–H), 1767.6 cm^{-1} (C=O); δ_H (CD_3CN, 200 MHz) 1.51 (d, 3H, H-6, $J_{5,6}=7.2$ Hz), 4.11 (s, 1H,

H-2), 4.45 (dd, 1H, H-4, $J_{3,4}=2.5$ Hz, $J_{4,5}=1.3$ Hz), 4.54 (dq, 1H, H-5, $J_{4,5}=0.6$ Hz, $J_{5,6}=7.2$ Hz), 4.63 (dd, 1H, H-3, $J_{2,3}=0.6$ Hz, $J_{3,4}=2.6$ Hz), 5.89 (s, 1H, PhC*H*), 7.35–7.41 (m, 5H, Ph); δ_C (CD_3CN, 50.3 MHz) 15.3 (C-6), 70.1 (C-5), 73.8 (C-2), 75.5 (C-3), 77.5 (C-4), 92.8 (Ph*C*H), 127.1, 129.2, 130.0 (Ph), 139.0 (C_{ipso}), 175.6 (C-1). Found: C, 62.10; H, 5.78; $C_{13}H_{14}O_5$ requires: C, 62.39; H, 5.64%.

*4.5. (*R*)-3,5-*O*-Benzylidene-6-deoxy-2-*O*-trifluoromethanesulfonyl-L-glucono-1,4-lactone **9** and (S)-3,5-O-benzylidene-6-deoxy-2-O-trifluoromethanesulfonyl-L-glucono-1,4-lactone **10***

Pyridine (0.40 ml, 5.0 mmol) was added to a solution of the *glucono*-lactone (0.24 g, 0.97 mmol) in THF (10 ml) under nitrogen at −78°C. Triflic anhydride (0.33 ml, 2.0 mmol) was added dropwise, and the mixture was stirred at −78°C for a further 15 min, before warming to 0°C. After 3.75 h, TLC (ethyl acetate:hexane, 2:1) revealed that the starting material (R_F 0.47) had been partially replaced by one product (R_F 0.7). The reaction mixture was recooled to −78°C; more pyridine (0.08 ml, 1.0 mmol) and triflic anhydride (0.17 ml, 1.0 mmol) were added. After 15 min, the reaction mixture was warmed to 0°C; TLC revealed that all the starting material had been consumed after 40 min. The reaction mixture was diluted with dichloromethane (20 ml), washed with 0.1 M hydrochloric acid (10 ml), and then water (10 ml). The organic fraction was dried ($MgSO_4$), filtered and the solvent was removed. The residue was dissolved in ethyl acetate, filtered through a plug of silica, and the solvent was removed to give the (*R*)-3,5-*O*-benzylidene triflate **9** (0.36 g, 98%), m.p. 70–72°C; ν_{max} (NaCl) 1803 cm^{-1} (C=O); δ_H (CD_3CN, 200 MHz) 1.52 (d, 3H, H-6, $J_{5,6}=7.0$ Hz), 4.57 (dq, 1H, H-5, $J_{4,5}=2.0$ Hz, $J_{5,6}=7.0$ Hz), 4.64 (dd, 1H, H-4, $J_{3,4}\approx J_{4,5}\approx 2.6$ Hz), 5.16 (dd, 1H, H-3, $J_{2,3}=1.4$ Hz, $J_{3,4}=2.8$ Hz), 5.32 (bs, 1H, H-2), 5.97 (s, 1H, PhCH), 7.38–7.49 (m, 5H, Ph); δ_C (CD_3CN, 50.3 MHz) 15.5 (C-6), 69.4, 73.2, 78.0, 82.1 (C-2, C-3,C-4, C-5), 93.7 (PhCH), 127.1, 129.3, 130.3 (Ph), 138.4 (C_{ipso}), 168.4 (C-1).

In a closely analogous procedure starting from 3,5-*O*-benzylidene-6-deoxy-L-*glucono*-1,4-lactone (0.20 g, 0.79 mmol), the crude material **9** was purified by flash chromatography (ethyl acetate:hexane, 1:4) to give the 3,5-*O*-(*R*)-benzylidene triflate **9** (0.07 g, 24%) and the (*S*)-3,5-*O*-benzylidene triflate **10** (0.014 g, 5%), m.p. 84–87°C; $[\alpha]_D^{22}$ −44.2 (*c* 0.995 in $CHCl_3$); ν_{max} (NaCl) 1806 cm^{-1} (C=O); δ_H (CD_3CN, 200 MHz) 1.40 (d, 3H, H-6, $J_{5,6}=6.0$ Hz), 4.08 (dq, 1H, H-5, $J_{4,5}=10.0$ Hz, $J_{5,6}=6.2$ Hz), 4.45 (dd, 1H, H-4, $J_{3,4}=8.0$ Hz, $J_{4,5}=10.2$ Hz), 5.22 (dd, 1H, H-3, $J_{2,3}=9.4$ Hz, $J_{3,4}=8.0$ Hz), 5.95 (s, 1H, PhCH), 6.28 (d, 1H, H-2, $J_{2,3}=9.8$ Hz), 7.40–7.51 (m, 5H, Ph); δ_C (CD_3CN, 50.3 MHz) 19.1 (C-6), 73.1 (C-4), 2×74.8 (C-3, C-5), 78.8 (C-2), 96.9 (PhCH), 127.1, 129.4, 130.4 (Ph), 137.5 (C_{ipso}), 167.0 (C-1). Found: C, 43.58; H, 3.73; $C_{14}H_{15}F_3O_7S$ requires: C, 43.98; H, 3.43%.

Due to the instability of **9** and its partial decomposition and epimerisation to **10**, the ratio of the benzylidene derivatives **9** and **10**, and yields of products, depend on the conditions under which **9** is handled. In contrast **10** is relatively stable and easy to handle.

*4.6. Methyl 2,4-anhydro-(*R*)-3,5-O-benzylidene-L-rhamnonate **3** and methyl 2,4-anhydro-(S)-3,5-O-benzylidene-L-rhamnonate **11***

*4.6.1. From the triflate of the (*R*)-benzylidene gluconolactone **9***

Potassium carbonate (0.46 g, 3.32 mmol) was added to a solution of crude (*R*)-benzylidene triflate **9** (0.63 g, 1.66 mmol) in methanol (14 ml, HPLC grade) at −78°C under nitrogen. The

solution was stirred for 1.3 h, and then diluted with dichloromethane (150 ml). The reaction mixture was washed with water (3×75 ml), the aqueous fractions combined and further extracted with dichloromethane (75 ml). All the organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate:hexane, 1:2) to give two products, the 3,5-*O*-(*R*)-benzylidene oxetane **3** (R_F 0.46, 0.236 g, 54%) (for data see above), and the 3,5-*O*-(*S*)-benzylidene oxetane **11** (R_F 0.33, 0.038 g, 9%), m.p. 62–63°C; $[\alpha]_D^{22}$ −33.9 (*c* 1.01 in $CHCl_3$); ν_{max} (NaCl) 1754.5 cm^{-1} (C=O); δ_H ($CDCl_3$, 400 MHz) 1.42 (d, 3H, H-6, $J_{5,6}=6.4$ Hz), 3.82 (s, 3H, CO_2Me), 4.44 (dq, 1H, H-5, $J_{4,5}=6.2$ Hz, $J_{5,6}=6.3$ Hz), 4.55 (ddd, 1H, H-4, $J_{2,4}=1.0$ Hz, $J_{3,4}=7.4$ Hz, $J_{4,5}=6.2$ Hz), 5.05 (dd, 1H, H-3, $J_{2,3}=6.2$ Hz, $J_{3,4}=7.4$ Hz), 5.53 (d, 1H, H-2, $J_{2,3}=6.0$ Hz), 6.16 (s, 1H, PhCH), 7.36–7.41 (m, 3H, Ph), 7.50–7.53 (m, 2H, Ph); δ_C ($CDCl_3$, 100.6 MHz) 20.17 (C-6), 52.57 (CO_2CH_3), 70.54 (C-3), 77.79 (C-5), 79.31 (C-4), 81.67 (C-2), 97.10 (PhCH), 126.32, 128.48, 129.39 (Ph), 137.27 (C_{ipso}), 170.44 (C-1).

4.6.2. From the triflate of the (S)-benzylidene gluconolactone ***10***

Potassium carbonate (0.10 g, 0.72 mmol) was added to a solution of the (*S*)-benzylidene triflate **10** (0.17 g, 0.45 mmol) in methanol (3.5 ml, HPLC grade) at −78°C under nitrogen. The solution was stirred for 1 h, when TLC (ethyl acetate:hexane, 1:1) showed that the starting material (R_F 0.71) had been replaced by a major product (R_F 0.57). The solution was diluted in dichloromethane (40 ml), washed with water (2×20 ml), dried ($MgSO_4$), filtered and the solvent removed to give the 3,5-*O*-(*S*)-benzylidene oxetane **11** (0.088 g, 74%), identical to the material above.

4.6.3. From the oxetane diol ***7***

Benzaldehyde dimethyl acetal (0.17 ml, 1.08 mmol) and tosic acid (2 mg) were added to a solution of oxetane diol **7** (0.032 g, 0.18 mmol) in DMF (1 ml) under nitrogen at room temperature. After 6 days, TLC (ethyl acetate:hexane, 1:1) revealed that some of the starting material (R_F 0.21) had been transformed into two products (R_F 0.5 and 0.64). The solution was neutralised over sodium carbonate, filtered and the solvent removed. The residue (0.050 g) was shown by ^1H NMR analysis to contain a 1:4 mixture of 3,5-*O*-(*R*)-benzylidene:3,5-*O*-(*S*)-benzylidene methyl-2,4-anhydro-L-rhamnonate.

4.7. Methyl 2,4-anhydro-L-rhamnonate ***7***

The benzylidene-protected oxetane **3** (0.417g, 1.58 mmol) was added to a solution of acetyl chloride (0.16 ml) in methanol (16 ml) at room temperature. After 1 h, TLC (ethyl acetate:hexane, 1:1) revealed the absence of starting material (R_F 0.5) and the presence of a major product (R_F 0.25). The solution was neutralised with sodium carbonate, filtered, and the solvent was removed. The crude material was purified by flash chromatography (ethyl acetate:hexane, 2:1), giving methyl-2,4-anhydro-L-rhamnonate (0.17 g, 54%); m.p. 52–54°C; $[\alpha]_D^{22}$ +84.6 (*c* 0.94 in $CHCl_3$); ν_{max} (NaCl) 1738 cm^{-1} (C=O), 2956 cm^{-1} (C–H), 3412 cm^{-1} (O–H); δ_H ($CDCl_3$, 200 MHz) 1.31 (d, 3H, H-6, $J_{5,6}=7.0$ Hz), 3.15 (bs, 1H, OH (C-5)), 3.81 (s, 3H, CO_2Me), 3.41 (bm, 1H, H-5), 4.52 (d, 1H, OH (C-3), $J_{3,OH}=10.0$ Hz), 4.59 (ddd, 1H, H-4, $J_{2,4}=0.9$ Hz, $J_{3,4}=6.8$ Hz, $J_{4,5}=4.0$ Hz), 4.83 (ddd, 1H, H-3, $J_{3,OH}=9.9$ Hz, $J_{2,3}=5.1$ Hz, $J_{3,4}=6.7$ Hz), 5.03 (dd, 1H, H-2, $J_{2,3}=4.8$ Hz, $J_{2,4}=0.8$ Hz); δ_C ($CDCl_3$, 50.3 MHz) 17.5 (C-6), 52.6 (CO_2CH_3), 69.5 (C-5), 71.6 (C-3), 86.7 (C-2), 86.9 (C-4), 171.1 (C-1); MS (APCI+) *m*/*z*: 117 (100%), 177: (MH^+, 30%). Found: C, 47.24; H, 6.76; $C_7H_{12}O_5$ requires: C, 47.73; H, 6.87%.

4.8. X-ray crystal structure analysis

The relative configurations of the stereogenic centres in the lactone **2** and the oxetane **11** were established by X-ray single crystal structure analysis. Cell dimensions and intensity data were measured with an Enraf–Nonius Mach3 Diffractometer, and Lorentz, polarisation and psi scan absorption corrections were applied. All calculations were carried out on a 486PC computer. All non-hydrogen atoms were located by SIR-92[24] and refined using CRYSTALS.[25] Illustrations were produced using CAMERON.[26] The hydroxyl hydrogen atom was located from a difference Fourier map, all other hydrogen atoms were seen in the difference density map but placed geometrically. Non-hydrogen atoms were refined anisotropically using atomic scattering factors from International Tables.[27] Larsen extinction correction and Chebychev weighting were used. Structural data for **2** and **11** have been deposited at the Cambridge Crystallographic Data Centre.[28]

4.8.1. Crystal data for lactone **2**

Crystallised from ethyl acetate/hexane to give colourless prisms, $C_{13}H_{14}O_5$, M 250.25. Monoclinic $P2_1$; a, 5.244(2); b, 9.360(5); c, 12.077(7) Å; α, 90; β, 99.96(5); γ, 90°; V, 583.8 Å^3; $Z=2$; crystal size, 0.2×0.2×0.8 mm; μ, 0.924 mm^{-1}; diffractometer, Nonius MACH3; Cu–Kα, 1.54180 Å; T, 190 K; scan type, $2\theta/\Omega$; h, −1 to 6; k, −3 to 11; l, −15 to 14. Refinement on F, 1209 reflections [$I>3\sigma(I)$]; R, 0.064; wR, 0.080; S, 0.952; $\Delta\rho_{max}$, 0.32 (e Å^{-3}); $\Delta\rho_{min}$, −0.30 (e Å^{-3}); $(\Delta/s)_{max}$, 0.000161.

4.8.2. Crystal data for oxetane **11**

Crystallised from ethyl acetate/hexane to give colourless blocks, $C_{14}H_{16}O_5$; M, 264.28. Orthorhombic $P2_12_12_1$; a, 4.870(2); b, 10.189(5); c, 27.382(7) Å; α, 90; β, 90; γ, 90°; V, 1358.5 Å^3; $Z=4$; crystal size, 0.5×0.9×0.9 mm; μ, 0.821 mm^{-1}; diffractometer, Nonius MACH3; Cu–Kα, 1.54180 Å; T, 293 K; scan type, $2\theta/\Omega$; h, 0–6; k, 0–12; l, −34 to 0. Refinement on F, 1631 reflections [$I>3\sigma(I)$]; R, 0.042; wR, 0.055; S, 0.855; $\Delta\rho_{max}$, 0.13 e Å^{-3}; $\Delta\rho_{min}$, −0.18 e Å^{-3}; $(\Delta/s)_{max}$, 0.0013.

Acknowledgements

An EPSRC ROPA post-doctoral fellowship supported this work.

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28. The atomic coordinates for **2** and **11** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.