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Oxetane *cis*- and *trans*-β-amino-acid scaffolds from L-rhamnose by efficient S_N2 reactions in oxetane rings; pseudoenantiomeric analogues of the antibiotic oxetin

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Abstract—An efficient multigram ring contraction of a 1,4-lactone 2-*O*-triflate derived from L-rhamnose—with *retention* of configuration in the ring closure—is the key step in the preparation of a series of oxetanes, which are pseudoenantiomeric analogues of the naturally occurring antibiotic oxetin, an oxetane *cis*-β-amino acid. Subsequent nucleophilic displacements of the corresponding triflates by azide proceed in consistently excellent yields, without any elimination, to provide syntheses of scaffolds for analogues of the antibiotic.

1. Introduction

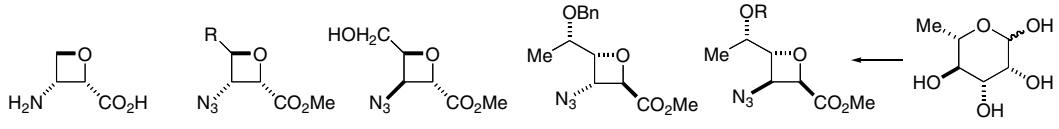
Oxetin **1**, a naturally occurring antibiotic,[1] is a *cis*-β-amino acid containing an oxetane ring; the preceding paper[2] reports the synthesis of a series of *cis*-**2** and **3** and *trans*-**4** analogues in which the absolute configuration at C-2 of the oxetane ring is the same as that in oxetin. Oligomers of the *cis*-amino acids **2** and **3** form a unique right-handed 10-helix. This is in marked contrast to other helical structures derived from oligomers of *trans*-cyclohexane, cyclopentane and pyrrolidine β-amino acid scaffolds.[3] Pseudoenantiomers of such β-amino acid oxetane oligomers afford left-handed 10-helical structures.

Herein we report the synthesis of protected derivatives of the *cis*- and *trans*-β-azido-oxetane-2-carboxylates **5**–**7** from L-rhamnose **8** as scaffolds, which are pseudoenantiomeric with oxetin and the analogues reported in the preceding paper. Some of this work has been reported in a preliminary form.[4,5]

2. Results and discussion

The key steps in the synthesis of the required silyl- and benzyl-protected azidoester scaffolds **5**–**7** are (i) the ring contraction of a suitably protected rhamnose derivative **10** to the oxetane **11** and (ii) the subsequent nucleophilic displacements of the C-3 oxygen function to introduce the azido function with inversion or retention of configuration (Scheme 1).

The conversion of L-rhamnose **8** to benzylidene oxetane **11** was performed with minor modifications to the previously reported procedure[6]—but on a larger scale and in



1 oxetin
2 R = CH_2OH
3 R = Me
4
5
6 R = TBDMS
7 R = Bn
8 L-rhamnose

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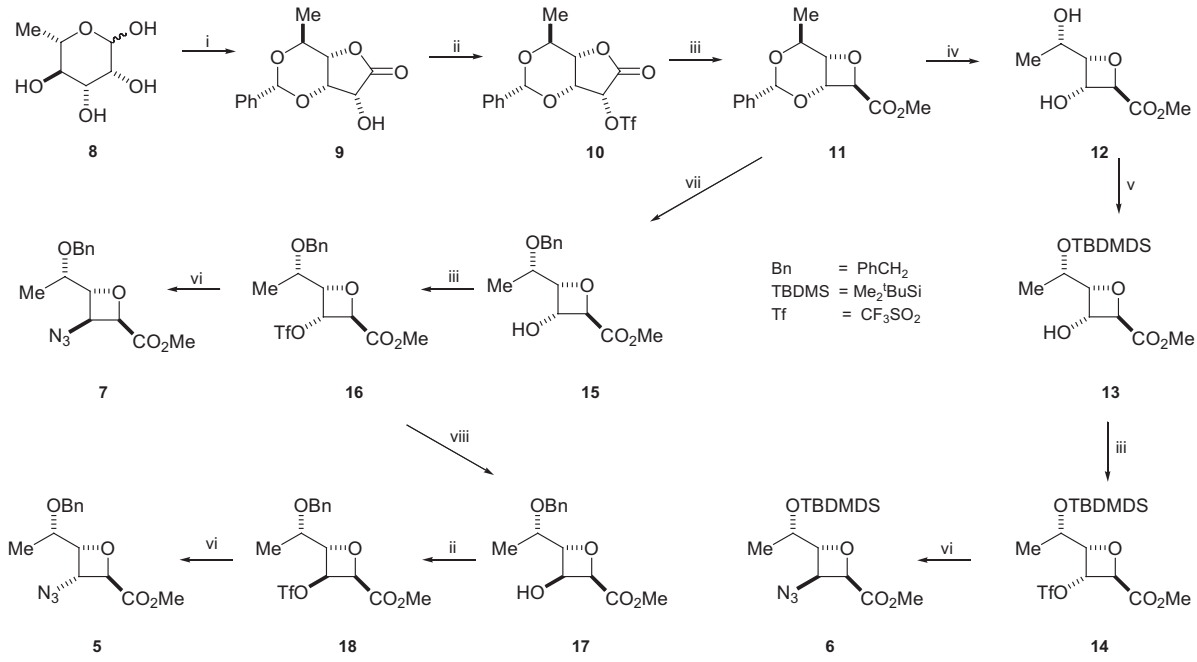

Scheme 1. Reagents and conditions: (i) Br_2, $BaCO_3$, H_2O, 0 °C to rt; then PhCHO, concd HCl, rt (72% over two steps); (ii) Tf_2O, pyridine, THF, −78 to 0 °C; (iii) K_2CO_3, MeOH, MeCN, −78 to −10 °C (89%); (iv) HCl, MeOH, rt (70%); (v) TBDMSCl, imidazole, DMF, 0 °C (31%); (vi) NaN_3, DMF, rt; (vii) Et_3SiH, CF_3CO_2H, CH_2Cl_2, rt (82%); (viii) $CsOCOCF_3$, MeCOEt, 70 °C (90%).

higher yield (60% overall yield on a 5 g scale). In the case of the L-rhamnose triflate **10**, however, the triflate of the γ-lactone is *cis* to the C-3 substituent. Oxidation of L-rhamnose **8** with bromine water buffered by barium carbonate gave a mixture of open chain acid and lactones; removal of the solvent followed by treatment of the crude residue with benzaldehyde in the presence of concentrated hydrochloride acid gave the benzylidene lactone **9**, easily purified by crystallisation, in 72% overall yield. Esterification of **9** with trifluoromethanesulfonic (triflic) anhydride afforded triflate **10** as a stable white solid, readily prepared on a 15 g scale. As illustrated in the preceding paper,[2] oxetanes can be readily formed by the ring contraction of suitably protected α-triflates of γ-lactones with basic methanol in good yield, providing that the triflate is *trans* to the oxygen substituent at C-3. The ring contraction of triflate **10** to oxetane **11** therefore required closure of the ring with overall retention of configuration during the nucleophilic displacement; this probably involved epimerisation of an open chain triflate ester. After careful optimisation of the reaction conditions, treatment of 6.8 g of **10** with potassium carbonate in methanol/acetonitrile gave the 2,3-*trans*-substituted oxetane **11** in 89% yield.

Structural studies on oligomers of the scaffolds required the use of a protecting group with no chromophores so that the *tert*-butyldimethyl silyl (TBDMS) scaffold **6** was chosen as the initial target. Treatment of benzylidene acetal **11** with hydrogen chloride in methanol afforded diol **12** (70% yield). Attempts to discriminate between the two secondary hydroxyl group in the diol **12** with TBDMS chloride and imidazole in DMF at 0 °C were unsuccessful. The desired 5-*O*-silyl ether **13** was formed in only 30% yield, along with the corresponding 3-*O*-silyl and disilyl compounds, both in approximately 10% yield.[7] No significant improvement in selectivity was achieved on attempted optimisation of the reaction. Activation towards nucleophilic substitution of the 3-OH in **13** with triflic anhydride and pyridine in dichloromethane gave triflate **14** (76% yield), which on subsequent reaction with sodium azide in DMF afforded the TBDMS protected azide **6** in 96% yield.

For the 5-*O*-benzyl protected scaffolds **5** and **7**, reduction of acetal **11** with triethylsilane and trifluoroacetic acid[8] in dichloromethane gave highly regioselective ring opening of the acetal with no reduction of the oxetane ring, producing the 5-*O*-benzyl protected oxetane **15** in 82% yield. A series of efficient S_N2 displacements of the activated 3-hydroxyl group in **15** gave access to the *cis* and *trans* benzyl-protected β-azido oxetane carboxylates. Reaction of **15** with triflic anhydride gave the corresponding triflate **16** in 96% yield. Treatment of triflate **16** with sodium azide in DMF gave the 2,3-*cis* azido ester **7** (97% yield), whereas reaction of **16** with caesium trifluoroacetate gave the *altrono*-alcohol **17** in 90% yield. Subsequent esterification of **17** with triflic anhydride gave triflate **18** in 99% yield, which upon treatment with sodium azide gave the 2,3-*trans* azido ester **5** in 87% yield (74% over four steps from **15**). This is a noteworthy set of efficient S_N2 displacements in oxetane rings with no sign of any competing elimination reactions.

3. Conclusions

Herein we have reported the synthesis of oxetane *cis*- and *trans*-β-azidoesters with silyl and benzyl protection, which are peptidomimetics likely to provide access to

homooligomers with novel secondary structure; these materials are pseudoenantiomeric with the amino acids formed from D-xylose in the preceding paper.[2] The synthesis of oligomers from both series, together with detailed structural studies by NMR, infrared and circular dichroism 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. 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 parts per million and coupling constants (J) in hertz. Residual signals from the solvents were used as internal references. ^{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. 3,5-(*R*)-*O*-Benzylidene-L-rhamnono-1,4-lactone 9

Barium carbonate (104.4 g, 1.5 equiv) was added to a stirred solution of L-rhamnose monohydrate **8** (48.45 g, 266 mmol) in water (360 mL) at 0 °C. Bromine (20.4 mL, 1.5 equiv) was added to the reaction mixture in four portions (4 × 5.1 mL) at 15 min intervals. The reaction mixture was stirred at 0 °C for 2 h, and then allowed to warm to room temperature and stirred overnight. TLC (EtOAc/MeOH 9:1) revealed that the starting material (R_f 0.23) had been completely consumed, and been replaced by major (R_f 0.36) and minor (R_f 0.46) products. The reaction mixture was then filtered through celite®. Nitrogen was passed through the filtrate until the solution was decolourised; the solvent was removed to yield the crude product (170.2 g). The crude solid (164.3 g) was suspended in benzaldehyde (475 mL), and concentrated hydrochloric acid (142 mL) added; the mixture was stirred at room temperature to afford after 2 days a major product (EtOAc/hexane, 2:1, R_f 0.27). The reaction mixture was filtered and approximately half the solvent removed; diethyl ether was added until the product crystallised out. The solid was then filtered and washed with Et_2O. The washings were re-concentrated, and more material was crystallised out to give, after three re-crystallisations, the benzylidene lactone **9** (45.8 g, 72%), with physical properties identical to those previously described,[6] mp 175–177 °C; $[\alpha]_D^{22} = -48.7$ (c 0.99 in MeCN).

4.2. 3,5-(*R*)-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-L-rhamnono-1,4-lactone 10

Pyridine (17.46 mL, 5 equiv) was added to a solution of benzylidene lactone **9** (10.52 g, 42 mmol) in THF (220 mL) under nitrogen at −78 °C. Trifluoromethanesulfonic (triflic) anhydride (14.63 mL, 2 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for a further 20 min, and then allowed to warm to 0 °C. After 1.5 h, TLC (EtOAc/hexane, 2:1) revealed that the starting material (R_f 0.21) had been completely replaced by one product (R_f 0.55). The reaction mixture was then diluted with dichloromethane (400 mL), washed with aqueous hydrochloric acid (0.1 M, 200 mL) and water (200 mL). The organic extract was dried over magnesium sulfate and the solvent removed. The crude product was purified by flash chromatography (EtOAc/hexane, 1:1) to give triflate **10** (14.78 g, 92%) as a white solid, with physical properties identical to those previously described.[6] Mp 139–140 °C; $[\alpha]_D^{22} = -63.9$ (c 0.98 in MeCN).

4.3. Methyl 2,4-anhydro-3,5-(*R*)-*O*-benzylidene-L-rhamnonate 11

A solution of triflate **10** (6.79 g, 17.8 mmol) in acetonitrile (25 mL) was added to potassium carbonate (4.97 g, 2 equiv) in methanol (140 mL) and stirred at −78 °C under nitrogen. The reaction mixture was then stirred

for 10 min, at which point it was warmed to −30 °C, then allowed to warm slowly to −10 °C over the following 30 min. The reaction mixture was then diluted with dichloromethane (340 mL). The starting material **10** and the product **11** were indistinguishable by TLC (EtOAc/hexane, 1:1, R_f 0.48). The reaction mixture was washed with water (2 × 170 mL), the aqueous fractions combined and then extracted with dichloromethane (170 mL). The organic fractions were combined, dried over magnesium sulfate and the solvent removed to give benzylidene oxetane **11** (4.20 g, 89% yield), mp 126–127 °C [Lit.[6] Mp 115–116 °C]; $[\alpha]_D^{23} = +3.0$ (*c* 1.01 in $CHCl_3$) {Lit.[6] $[\alpha]_D^{23} = +3.0$ (*c* 1.01 in $CHCl_3$)}.

4.4. Methyl 2,4-anhydro-L-rhamnonate 12

Benzylidene acetal **11** (500 mg, 1.89 mmol) was added in one portion to a mixture of acetyl chloride (80 μL) and methanol (8 mL). After 10 min, TLC (EtOAc/hex, 1:1) showed the consumption of the starting material (R_f 0.47) and the appearance of a single spot (R_f 0.09). The mixture was then neutralised with sodium bicarbonate, filtered and evaporated to dryness. Column chromatography (acetone/hexane, 1:2 → 1:1) afforded diol **12** as a clear oil, which solidified upon standing and had identical physical properties to those previously described.[6] Mp 52–54 °C; $[\alpha]_D^{22} = +84.6$ (*c* 0.94 in $CHCl_3$).

4.5. Methyl 2,4-anhydro-5-*O*-*tert*-butyldimethylsilyl-L-rhamnonate 13

tert-Butyldimethylsilyl chloride (171 mg, 1.35 mmol) was added to a solution of the diol **12** (200 mg, 1.13 mmol) and imidazole (81 mg, 1.19 mmol) in DMF (10 mL) at 0 °C under an inert atmosphere. After 2 h TLC indicated the presence of a major compound (R_f 0.38, EtOAc/hexane, 1:3). The reaction mixture was diluted with EtOAc (30 mL), washed with H_2O (10 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (EtOAc/hexane, 1:3) afforded silyl ether **13** as a clear oil, which solidified upon standing (102 mg, 31%). Found: C, 53.73, H, 9.05; $C_{13}H_{26}O_5Si$ requires: C, 53.76, H, 9.02; mp 49–51 °C; $[\alpha]_D^{22} = +0.65$ (*c* 0.8 in $CHCl_3$); ν_{max} (thin film) 3461 (OH), 1756 (C=O); δ_H (200 MHz, $CDCl_3$): 0.22 (2 × s, 6H, $Si(CH_3)_2$), 1.02 (s, 9H, $SiC(CH_3)_3$), 1.32 (d, 3H, $J_{6,5}$ 6.8 Hz, H-6), 3.86 (s, 3H, CO_2Me), 4.26 (ddd, 1H, $J_{5,6} = J_{5,4}$ 6.8, $J_{5,3}$ 1.8 Hz, H-5), 4.62 (ddd, 1H, $J_{4,5}$ 6.8, $J_{4,3}$ 1.8 $J_{4,2}$ 0.6 Hz, H-4), 4.79 (sept, 1H, $J_{3,OH}$ 11.8, $J_{3,2}$ 5.0, $J_{3,4}$ 1.8 Hz, H-3), 4.98 (dd, 1H, $J_{2,3}$ 5.0, $J_{2,4}$ 0.6 Hz, H-2), 5.10 (d, 1H, $J_{OH,3}$ 11.8 Hz, 3-OH); δ_C (50.3 MHz, $CDCl_3$): −4.5 ($Si(CH_3)_2$), 18.3 (C-6), 19.1 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 52.7 (CO_2CH_3), 72.5, 72.8 (C-3/5), 87.2 (C-2), 87.6 (C-4), 171.5 (C=O); *m*/*z* (CI+): 313 [M+Na] (35%), 291 [M+H] (30), 158 (100).

4.6. Methyl 2,4-anhydro-5-*O*-*tert*-butyldimethylsilyl-3-*O*-trifluoromethanesulfonyl-L-rhamnonate 14

Triflic anhydride (127 μL, 0.757 mmol) was added dropwise to a solution of silyl ether **13** (110 mg, 0.378 mmol) and pyridine (153 μL, 1.89 mmol) in dichloromethane (5 mL) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 20 min, and then at 0 °C for 1 h after which time TLC showed the formation of one major product (R_f 0.64, EtOAc/hexane, 1:3). The reaction mixture was then diluted with dichloromethane (30 mL), washed with water (5 mL), dried over $MgSO_4$ and the organic layer evaporated to dryness. Column chromatography (EtOAc/hexane, 1:5) afforded triflate **14** as a clear oil (122 mg, 76%). $[\alpha]_D^{22} = +17.7$ (*c* 1.13 in $CHCl_3$); ν_{max} (thin film): 1754 (C=O); δ_H (200 MHz, $CDCl_3$): 0.16 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.28 (d, 3H, $J_{6,5}$ 6.4 Hz, H-6), 3.90 (s, 3H, CO_2Me), 4.26–4.32 (m, 1H, H-5), 4.66 (ddd, 1H, $J_{4,5}$ 7.8, $J_{4,3}$ 6.9, $J_{4,2}$ 1.0 Hz, H-4), 5.16 (dd, 1H, $J_{2,3}$ 4.6, $J_{2,4}$ 1.0 Hz, H-2), 5.72 (dd, 1H, $J_{3,4}$ 6.9, $J_{3,2}$ 4.6 Hz, H-3); δ_C (50.3 MHz, $CDCl_3$): −5.5, −4.8 ($Si(CH_3)_2$), 17.2 ($SiC(CH_3)_3$), 17.7 (C-6), 25.0 ($SiC(CH_3)_3$), 52.1 (CO_2CH_3), 66.3 (C-5), 78.1, 80.7 (C-2/C-3), 85.3 (C-4), 114.5, 120.9 (*J* 322 Hz, SO_2CF_3), 167.6 (C=O); *m*/*z* (CI+): 445 [M+Na^+] (35%), 194 (100).

4.7. Methyl 2,4-anhydro-3-azido-5-*O*-*tert*-butyldimethylsilyl-3,6-dideoxy-L-altronate 6

Sodium azide (120 mg, 1.84 mmol) was added in one portion to a stirred solution of triflate **14** (600 mg, 1.42 mmol) in DMF (6 mL) at room temperature under an inert atmosphere. After 4 h no starting material remained and a single product (R_f 0.40, acetone/hexane, 1:5) had formed. The solvent was removed and the residue dissolved in ethyl acetate (60 mL); the reaction mixture was washed with water (15 mL) and dried over magnesium sulfate. Column chromatography (EtOAc/hexane, 1:5) of the crude product afforded *cis*-azide **6** as a clear oil (430 mg, 96%). Found C, 49.33, H, 7.99, N, 13.29; $C_{13}H_{25}N_3O_4Si$ requires: C, 49.50, H, 7.99, N, 13.32; $[\alpha]_D^{22} = -69.5$ (*c* 0.8 in $CHCl_3$); ν_{max} (thin film): 2111 (N_3), 1761 (C=O); δ_H (200 MHz, $CDCl_3$): 0.12 (s, 6H, $Si(CH_3)_2$), 0.97 (s, 9H, $SiC(CH_3)_3$), 1.13 (d, 3H, $J_{6,5}$ 6.5 Hz, H-6), 3.85 (s, 3H, CO_2Me), 3.97 (qd, 1H, $J_{5,6}$ 6.5, $J_{5,4}$ 2.7 Hz, H-5), 4.46 (ddd, 1H, $J_{4,3}$ 5.1, $J_{4,5}$ 2.7, $J_{4,2}$ 0.4 Hz, H-4), 4.82 (dd, 1H, $J_{3,2}$ 7.8, $J_{3,4}$ 5.1 Hz, H-3), 5.03 (d, 1H, $J_{2,3}$ 7.8 Hz, H-2); δ_C (50.3 MHz, $CDCl_3$): −3.9 ($Si(CH_3)_2$), 18.0 (C-6, $SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 52.2 (CO_2CH_3), 55.3 (C-3), 67.3 (C-5), 79.1 (C-4), 90.3 (C-2), 169.6 (C=O).

4.8. Methyl 2,4-anhydro-5-*O*-benzyl-L-rhamnonate 15

A solution of benzylidene oxetane **11** (0.946 g, 3.58 mmol) and triethylsilane (2.80 mL, 17.9 mmol) in dry dichloromethane (16 mL) was stirred under nitrogen at room temperature. Trifluoroacetic acid (1.37 mL, 17.9 mmol) was added dropwise over 5 min. After 105 min, TLC (EtOAc/hexane, 1:1) indicated the formation of a major product (R_f 0.35). Ethyl acetate (80 mL) was added to the reaction mixture, which was then washed with saturated sodium bicarbonate (30 mL) and then brine (30 mL). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography (EtOAc/hexane, 2:3) to give benzyl

ether **15** (0.784 g, 82% yield) as a white crystalline solid. Found C, 63.07; H, 6.82; $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%; HRMS *m/z* (CI+) Found 284.1492 ($M + NH_4^+$). $C_{14}H_{22}NO_5$ requires 284.1497; mp 40–42 °C; $[\alpha]_D^{23} = +69.7$ (*c* 1.1 in $CHCl_3$); ν_{max} (NaCl) 3462 cm^{-1} (OH) 2953 cm^{-1} (C-H), 1752 cm^{-1} (C=O); δ_H ($CDCl_3$, 200 MHz) 1.30 (d, 3H, H-6, $J_{5,6}$ = 6.9 Hz), 3.81 (s, 3H, –CO_2Me), 4.12 (dq, 1H, H-5, $J_{4,5}$ = 2.3 Hz, $J_{5,6}$ = 6.9 Hz), 4.64 (d, 1H, –O*H*, $J_{3,OH}$ = 11.7 Hz), 4.67–4.90 (m, 4H, H-3, H-4, –CH_2Ph), 5.09 (dd, 1H, H-2, $J_{2,3}$ = 5.4 Hz, $J_{2,4}$ = 0.7 Hz), 7.32–7.42 (m, 5H, Ph); δ_C ($CDCl_3$, 50.3 MHz) 15.2 (C-6), 52.2 (–CO_2CH_3), 71.7 (C-3), 72.8 (–CH_2Ph), 77.8 (C-5), 87.0 (C-2), 87.3 (C-4), 127.8–128.6 (Ph), 137.5 (C_{ipso}), 170.9 (C-1).

4.9. Methyl 2,4-anhydro-5-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-L-rhamnonate 16

Triflic anhydride (2.28 mL, 13.51 mmol) was added dropwise to a solution of alcohol **15** (2.00 g, 7.51 mmol) and pyridine (3.06 mL, 37.55 mmol) in dichloromethane (75 mL) at −78 °C under an atmosphere of argon. The reaction mixture was stirred for 30 min at −78 °C after which time the bath at −78 °C was changed for a bath at −30 °C. The temperature was then allowed to warm up to −10 °C taking 1.5 h. TLC (EtOAc/hexane, 3:7) revealed a single product (R_f 0.60) and no residual starting material (R_f 0.21). The reaction mixture was diluted with dichloromethane (300 mL) and washed with aqueous hydrochloric acid (0.1 M) and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:4) to give triflate **16** as an oil (2.88 g, 96%). Found C, 45.48; H, 4.28; $C_{15}H_{17}F_3O_7S$ requires C, 45.23; H, 4.30%; HRMS *m/z* (CI+) Found 416.0990 ($M + NH_4^+$), $C_{15}H_{21}NO_7F_3S$ requires 416.0990; $[\alpha]_D^{22} = +13.4$ (*c* 1.1 in $CHCl_3$); ν_{max} (thin film) 1760 (C=O ester) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.31 (d, 3H, $J_{5,6}$ 6.1 Hz, H-6), 3.86 (s, 3H, CO_2CH_3), 4.15 (dq, 1H, $J_{5,6}$ 6.1, $J_{4,5}$ 8.6 Hz, H-5), 4.56 (d, 1H, J_{gem} 11.0 Hz, CH*H*Ph), 4.63 (d, 1H, J_{gem} 11.0 Hz, CH*H*Ph), 4.75 (ddd, 1H, $J_{2,4}$ 1.1, $J_{3,4}$ 6.3, $J_{4,5}$ 8.6 Hz, H-4), 5.16 (dd, 1H, $J_{2,3}$ 4.5, $J_{2,4}$ 1.1 Hz, H-2), 5.72 (dd, 1H, $J_{2,3}$ 4.5, $J_{3,4}$ 6.3 Hz, H-3), 7.28–7.39 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz) 14.6 (C-6), 53.0 (CO_2CH_3), 70.7 (C-5), 72.0 (CH_2Ph), 79.3 (C-3), 81.1 (C-2), 84.3 (C-4), 118.3 (q, $J_{13C,19F}$ s Hz, CF_3), 127.7, 127.9, 128.3 (5C, Ph), 137.6 (C_{ipso}), 168.1 (C-1); *m/z* (CI+) 416 ($M + NH_4^+$, 100%).

4.10. Methyl 2,4-anhydro-3-azido-3,6-dideoxy-5-*O*-benzyl-L-altronate 7

Sodium azide (104 mg, 1.59 mmol) was added in one portion to a solution of L-rhamnono triflate **16** (394 mg, 0.99 mmol) in dimethylformamide (5 mL) under an atmosphere of argon when the starting material (R_f 0.60, EtOAc/hexane, 3:7) had been completely replaced by a new product (R_f 0.58). The solvent was removed in vacuo, the residue dissolved in ethyl acetate, washed with water and brine and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (EtOAc/hexane 1:4) to give **7** (280 mg, 97%) as a clear oil. $[\alpha]_D^{22} = -106.3$ (*c* 1.4 in $CHCl_3$); Found C, 57.82; H, 5.89; N, 14.47; $C_{14}H_{17}N_3O_4$ requires C, 57.72; H, 5.88; N, 14.42; ν_{max} (thin film) 2116 (N_3), 1760 (C=O ester) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.14 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6), 3.80 (dq, 1H, $J_{5,6}$ 6.6, $J_{4,5}$ 3.7 Hz, H-5), 3.87 (s, 3H, CO_2CH_3), 4.59 (ddd, 1H, $J_{2,4}$ 0.6, $J_{3,4}$ 5.4, $J_{4,5}$ 3.7 Hz, H-4), 4.68 (d, 1H, J_{gem} 11.5 Hz, CH*H*Ph), 4.72 (d, 1H, J_{gem} 11.5 Hz, CH*H*Ph), 4.84 (dd, 1H, $J_{2,3}$ 7.3, $J_{3,4}$ 5.4 Hz, H-3), 5.14 (br d, 1H, $J_{2,3}$ 7.3, H-2), 7.27–7.38 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz) 14.8 (C-6), 52.3 (CO_2CH_3), 56.2 (C-3), 72.2 (CH_2Ph), 73.6 (C-5), 79.2 (C-2), 92.3 (C-4), 127.6, 127.7, 127.8, 128.4 (5C, Ph), 138.3 (C_{ipso}), 169.5 (C-1); *m/z* (APCI+) 264 ($M+H^+-N_2$, 95%), 206 (90), 157 (50), 121 (100).

4.11. Methyl 2,4-anhydro-6-deoxy-5-*O*-benzyl-L-altronate 17

Caesium trifluoroacetate (6.90 g, 28.08 mmol) was added to a solution of triflate **16** (2.80 g, 7.02 mmol) in butanone (70 mL) under an atmosphere of argon. The reaction mixture was heated at 70 °C for 15 h after which TLC (EtOAc/hexane, 3:7) indicated that the starting material (R_f 0.60) had been replaced by a major product (R_f 0.11). The solvent was removed and the residue purified by flash chromatography (EtOAc/hexane, 1:2 → 1:1) to yield the inverted alcohol **17** as a white solid (1.68 g, 90%). Mp 93–94 °C; $[\alpha]_D^{22} = +30.5$ (*c* 0.5 in $CHCl_3$); Found C, 62.94; H, 6.78; $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81; ν_{max} (KBr plate) 3454 (OH), 1732 (C=O ester) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.15 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6), 3.78 (dq, 1H, $J_{5,6}$ 6.6, $J_{4,5}$ 3.6 Hz, H-5), 3.83 (s, 3H, CO_2CH_3), 4.66 (m, 1H, H-4), 4.68 (s, 2H, CH_2Ph), 4.95 (br dd, 1H, $J_{2,3}$ 7.2, $J_{3,4}$ 5.0 Hz, H-3), 5.07 (br d, 1H, $J_{2,3}$ 7.2, H-2), 7.25–7.38 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz) 14.8 (C-6), 52.2 (CO_2CH_3), 67.0 (C-3), 72.1 (CH_2Ph), 73.9 (C-5), 81.9 (C-2), 93.4 (C-4), 127.5, 127.6, 128.3 (5C, Ph), 138.5 (C_{ipso}), 170.7 (C-1); *m/z* (APCI+) 284 ($M + NH_4^+$, 10%), 267 ($M+H^+$, 65), 121 (100).

4.12. Methyl 2,4-anhydro-5-*O*-benzyl-6-deoxy-3-*O*-trifluoromethanesulfonyl-L-altronate 18

Triflic anhydride (1.36 mL, 8.09 mmol) was added dropwise to a solution of alcohol **17** (1.19 g, 4.49 mmol) and pyridine (1.83 mL, 22.45 mmol) in dichloromethane (30 mL) at −45 °C under an atmosphere of argon. The temperature was then allowed to warm up to −10 °C over 2 h. A single product (R_f 0.65, EtOAc/hexane, 3:7) was formed and all the starting material (R_f 0.11) had been consumed. The reaction mixture was diluted with dichloromethane (200 mL) and washed with aqueous hydrochloric acid (0.1 M) and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:9) to yield triflate **18** as an oil (1.78 g, 99%). $[\alpha]_D^{22} = -33.2$ (*c*, 0.9 in $CHCl_3$); HRMS *m/z* (CI+) Found 416.0989 ($M + NH_4^+$), $C_{15}H_{21}NO_7F_3S$ requires 416.0990; ν_{max} (thin film) 1766 (C=O ester) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 1.23 (d, 3H, $J_{5,6}$ 6.7 Hz, H-6), 3.91 (dq, 1H, $J_{5,6}$ 6.7, $J_{4,5}$ 2.9 Hz, H-5), 3.94 (s,

3H, CO_2CH_3), 4.75 (d, 1H, J_{gem} 11.5 Hz, CH*H*Ph), 4.80 (d, 1H, J_{gem} 11.5 Hz, CH*H*Ph), 4.96 (ddd, 1H, $J_{2,4}$ 1.2, $J_{3,4}$ 4.5, $J_{4.5}$ 2.9 Hz, H-4), 5.32 (dd, 1H, $J_{2.3}$ 6.7, $J_{2.4}$ 1.2 Hz, H-2), 5.92 (dd, 1H, $J_{2,3}$ 6.7, $J_{3,4}$ 4.5 Hz, H-3), 7.36–7.47 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz) 14.4 (C-6), 52.7 (CO_2CH_3), 72.4 (CH_2Ph), 73.1 (C-5), 77.1 (C-3), 78.8 (C-2), 90.0 (C-4), 118.2 (q, $J_{13C,19F}$ 320 Hz, CF_3), 127.6, 127.8, 128.4 (5C, Ph), 137.9 (C_{ipso}), 167.4 (C-1); *m/z* (CI+) 416 ($M + NH_4^+$, 100%).

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

Sodium azide (421 mg, 6.47 mmol) was added in one portion to a solution of *altrono*-triflate **18** (1.72 g, 4.32 mmol) in dimethylformamide (20 mL) under an atmosphere of argon. The reaction mixture was stirred for 14 h at room temperature when a single product (R_f 0.54, EtOAc/hexane 3:7) and no residual starting material (R_f 0.65) remained. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate and the organic layer washed with water, brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc/hexane 1:9 → 1:4) to give *trans*-azide **5** (1.10 g, 87%) as an oil. $[\alpha]_D^{22} = -30.0$ (*c* 1.0 in $CHCl_3$) [Found C, 57.87; H, 5.90; N, 14.44; $C_{14}H_{17}N_3O_4$ requires C, 57.72; H, 5.88; N, 14.42]; HRMS *m/z* (ESI$^+$) Found 314.1109 (M+Na$^+$), $C_{14}H_{17}N_3O_4Na$ requires 314.1117; ν_{max} (thin film) 2117 (N_3), 1758 (C=O ester) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 1.28 (d, 3H, $J_{5,6}$ 5.8 Hz, H-6), 3.85 (s, 3H, CO_2CH_3), 4.10 (dq, 1H, $J_{5,6}$ 5.8, $J_{4,5}$ 8.3 Hz, H-5), 4.56 (d, 1H, J_{gem} 10.9 Hz, CH*H*Ph), 4.61 (dd, 1H, $J_{3,4}$ 6.8, $J_{4.5}$ 8.3 Hz, H-4), 4.67 (d, 1H, J_{gem} 11.0 Hz, CH*H*Ph), 4.73 (dd, 1H, $J_{2.3}$ 5.6, $J_{3.4}$ 6.8 Hz, H-3), 4.85 (d, 1H, $J_{2,3}$ 5.6 Hz, H-2), 7.28–7.40 (m, 5H, PhH); δ_C ($CDCl_3$, 50.3 MHz) 15.3 (C-6), 53.2 (CO_2CH_3), 59.7 (C-3), 71.5 (CH_2Ph), 73.7 (C-5), 81.5 (C-2), 85.2 (C-4), 128.3, 128.6, 128.9 (5C, Ph), 138.4 (C_{ipso}), 170.7 (C-1); *m/z* (APCI+) 265 (17%), 264 ($M+H^+-N_2$, 100), 220 (17), 158 (80).

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