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Synthesis of all diastereomeric methyl 2,5-anhydro-3-deoxy-hexonates: precursors to *C*-2-deoxynucleosides and THF-templated γ- and δ-amino acids

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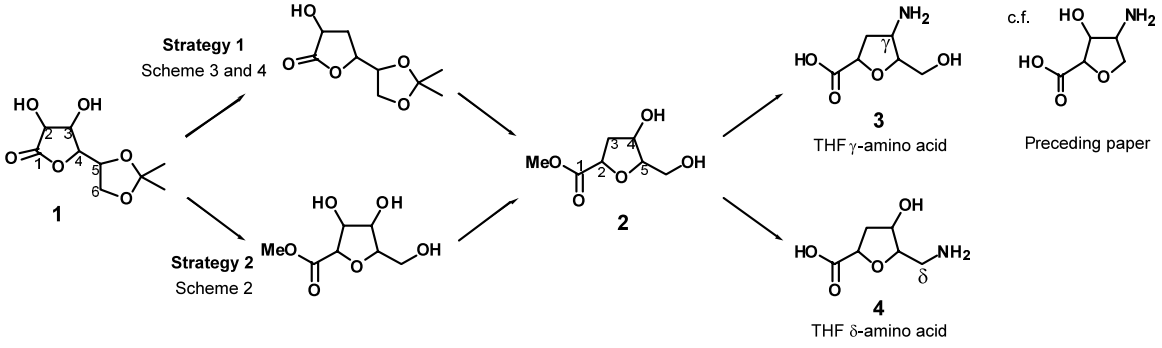
Abstract—Efficient syntheses of all diastereomers of methyl 2,5-anhydro-3-deoxy-hexonate from *mannono*- or *gulono*-lactones provide precursors for *C*-nucleosides of 2-deoxyribose and for THF-templated γ- and δ-amino acids.

1. Introduction

The preceding paper[1] described routes to tetrahydrofuran-templated γ-amino acids from pentono-1,5-lactones, as building blocks for carbopeptoids with predisposition towards well-defined secondary structures (foldamers).[2] This paper describes the synthesis of analogues **3** bearing a C-5 hydroxymethyl group from hexono-1,4-lactones (γ-lactones) **1** via 3-deoxy-THF-2-carboxylates **2** (Scheme 1). Sugar amino acids are an excellent source of stereodiverse polyfunctional scaffolds for the design of peptidomimetics[3,4] and combinatorial libraries thereof.[5,6] The THF-templated amino acids **3** and their regioisomers **4** provide three points for diversification with orthogonal chemical reactivity; libraries have been reported based on pyranose analogues having the same three functionalities[7] and with five points of diversification.[8] Additionally the THF-2-carboxylates **2** are of interest as intermediates for the synthesis of *C*-nucleosides of the stereoisomers of 2-deoxy-ribose.[9]

The THF-2-carboxylates **2** are accessible via the high yielding rearrangement of 2-*O*-sulfonate derivatives of 3-deoxy-γ-lactones under acidic conditions.[10] For the synthesis of THF γ-amino acids **3**, the γ-lactone structure **1** precludes introduction of a C-4 nitrogen substituent prior to the formation of the THF ring. Within this approach to THF γ-amino acids **3**, there is flexibility for C-3 deoxygenation either before (Strategy 1,



Scheme 1. Synthetic routes to THF-templated γ- and δ-amino acids from hexono-1,4-lactones.

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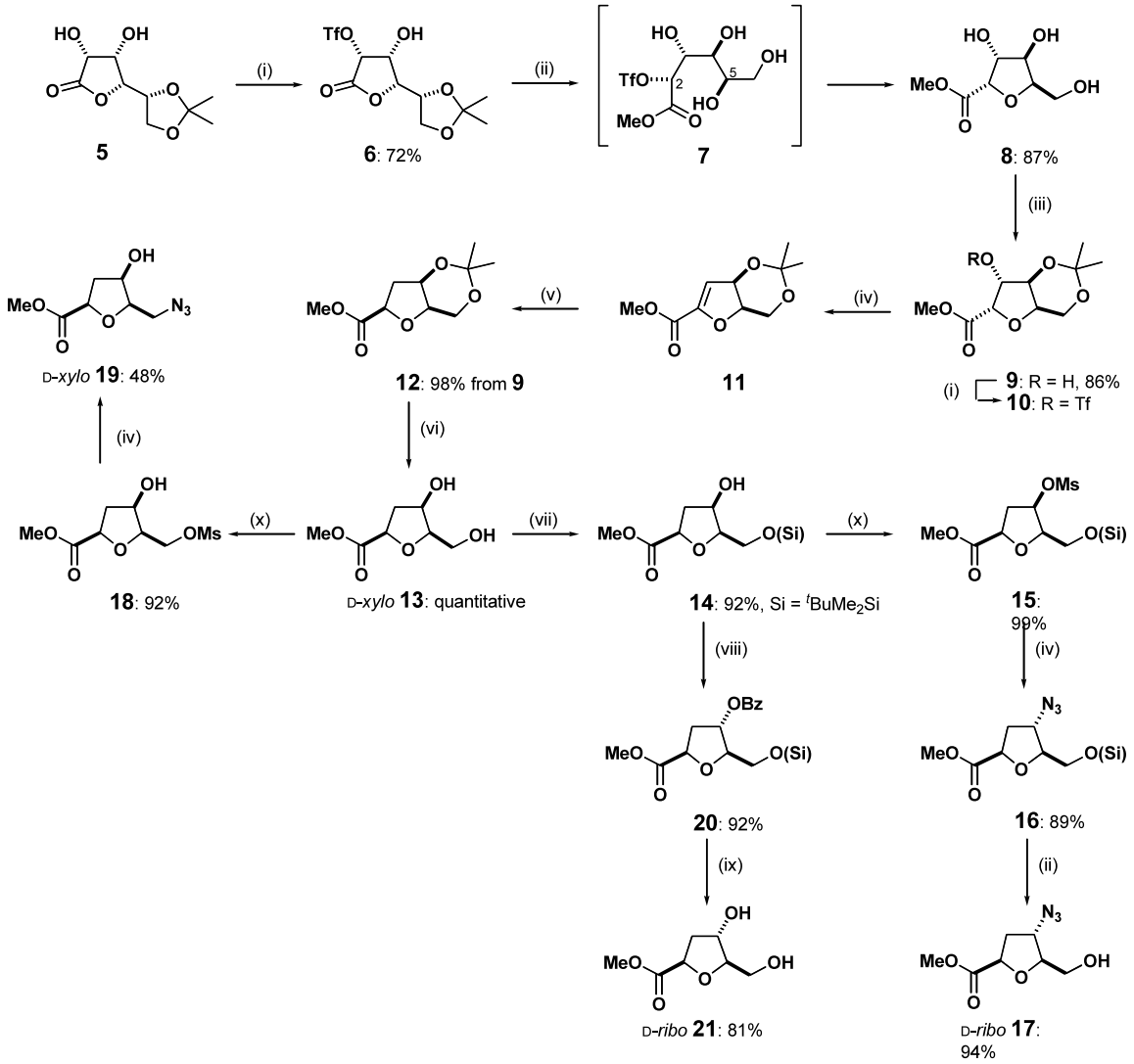
Scheme 1) or after (Strategy 2, Scheme 1) formation of the THF ring. Selective transformation of either the C-4 or C-6 functionality of the 3-deoxy-*C*-glycosyl derivative **2** provides access to THF-templated γ- and δ-amino acids **3** and **4**, respectively. The 3-deoxy THF δ-amino acids **4** provide further opportunities for evaluating the influence of ring stereochemistry[11] on the conformational properties of carbopeptoids derived from them. Routes to 2,5-anhydro-3-deoxy-D-*xylo*- and D-*ribo*-hexonic acids and an *O*-benzylated-D-*arabino* analogue[9b] have been reported previously from both carbohydrate[12] and non-carbohydrate[9a] starting materials. This paper describes the synthesis of derivatives of methyl 2,5-anhydro-3-deoxy-hexonates **2** of D-*xylo*, D-*ribo*, L-*lyxo* and L-*arabino* configuration and their conversion to all diastereomeric 4-azido and 6-azido derivatives, precursors to THF γ- and δ-amino acids **3** and **4**.

2. Strategy 1: Deoxygenation *after* THF formation. D-*ribo* γ-Azido ester 17 and D-*xylo* δ-azido ester 19

In the synthesis of the D-*xylo* THF-2-carboxylate **13** deoxygenation at the C-3 position of the carbohydrate skeleton was accomplished *after* formation of the THF ring (Scheme 2). Regioselective *O*-sulfonation of the kinetic monoacetonide **5** derived from D-gulono-1,4-lactone[13] with triflic anhydride at –40°C gave the stable triflate **6** {mp 103–104°C; $[\alpha]_D^{24}$ –15.7 (*c* 1.0)}[14] in 72% yield. Treatment with an acidic methanol solution converted the lactone **6** to the D-*ido* THF carboxylate **8** in 87% yield {oil; $[\alpha]_D^{24}$ –29.3 (*c* 1.3 in MeOH)} presumably via an open chain hydroxy triflate **7**. The 4,6-diol unit of **8** was subsequently protected as the isopropylidene ketal **9** in 86% yield {mp 93–95°C (ethyl acetate); $[\alpha]_D^{25}$ –29.5 (*c* 1.0 in MeOH)}. Activation of the C-3 hydroxyl group of **9** with triflic anhydride at



Scheme 2. *Reagents and conditions*: (i) Tf_2O, pyridine, DCM; (ii) HCl, MeOH; (iii) Me_2CO, $Me_2C(OMe)_2$, CSA; (iv) NaN_3, DMF; (v) H_2, Pd black, MeOH; (vi) 80% v/v aq. AcOH; (vii) $^tBuMe_2SiCl$, imidazole, DMF; (viii) DEAD, PPh_3, $PhCO_2H$, THF; (ix) HCl, MeOH then NaOMe, MeOH; (x) MsCl, DMAP, pyridine.

−30°C gave the unstable triflate **10** which was smoothly converted to the crude elimination product **11** on addition of sodium azide in DMF. No β-azido ester products arising from substitution of the triflate ester functionality were detected, in sharp contrast to an example given in the preceding paper.[1] Alkene **11** underwent stereoselective hydrogenation in the presence of a palladium catalyst to afford the fully protected D-*xylo* ester **12** {98% from **9**; oil; $[\alpha]_D^{20}$ −20.4 (*c* 1.0 in acetone)}. The 2,5-*cis*-stereochemistry of **12** was confirmed from NOE difference data.

Acidic hydrolysis of the isopropylidene moiety of **12** generated the D-*xylo* diol **13** {quantitative; mp 57–58°C (ethyl acetate); $[\alpha]_D^{23}$ −19.8 (*c* 1.0 in H_2O)} and derivatisation with *tert*-butyldimethylsilyl chloride and imidazole at 0°C occurred selectively to give a single monosilyated product **14** in 92% yield {mp 55–56°C; $[\alpha]_D^{26}$ +29.9 (*c* 1.1)}. Conversion of **14** to the mesylate **15** {99% yield; mp 64–65°C; $[\alpha]_D^{26}$ +67.4 (*c* 1.1)}, followed by treatment of **15** with sodium azide in DMF at 100°C generated the *O*-protected D-*ribo* γ-azido ester **16** in 89% yield {oil; $[\alpha]_D^{26}$ +15.8 (*c* 1.1)}. Acidic methanolysis of **16** gave the corresponding unprotected D-*ribo* target **17** in high yield (94%).[15] The D-*xylo* δ-azido ester **19**[16] was prepared from the D-*xylo* diol **13** in moderate yield (44% from **13**; oil; $[\alpha]_D^{23}$ −40.2 (*c* 1.4)} via azide displacement of the 6-*O*-methanesulfonyl intermediate **18** (92% from **13**; oil; $[\alpha]_D^{23}$ −29.0 (*c* 0.5)}.

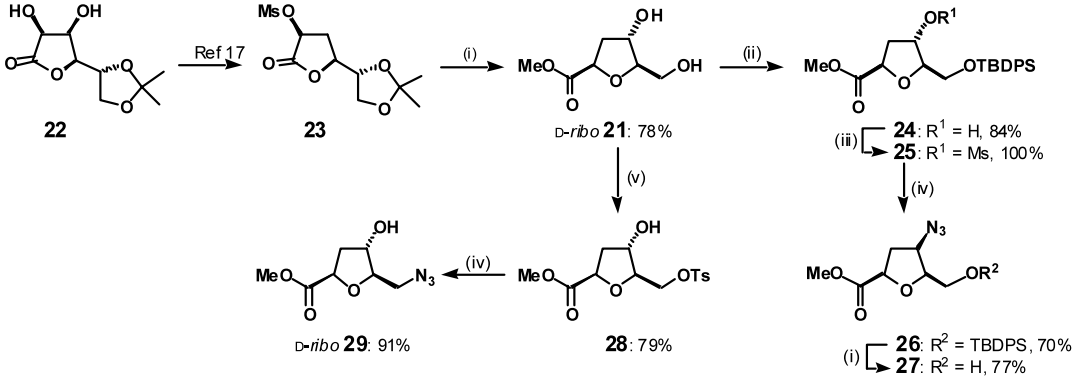
The silyl ether **14** was also used to prepare the D-*ribo* THF-2-carboxylate **21**, epimeric at C-4 to **13** (Scheme 2). Inversion of configuration at the C-4 position of **14** was performed in highest yield under Mitsunobu conditions to give the inversion ester **20** {92%; oil; $[\alpha]_D^{26}$ +13.7 (*c* 0.8)}. *O*-Deprotection of **20** by alternate treatment with acidic and basic methanol provided the D-*ribo* configured diol **21** {81% from **20**; oil; $[\alpha]_D^{24}$ +27.7 (*c* 0.8 in MeOH)}.

3. Strategy 2: Deoxygenation *before* THF formation

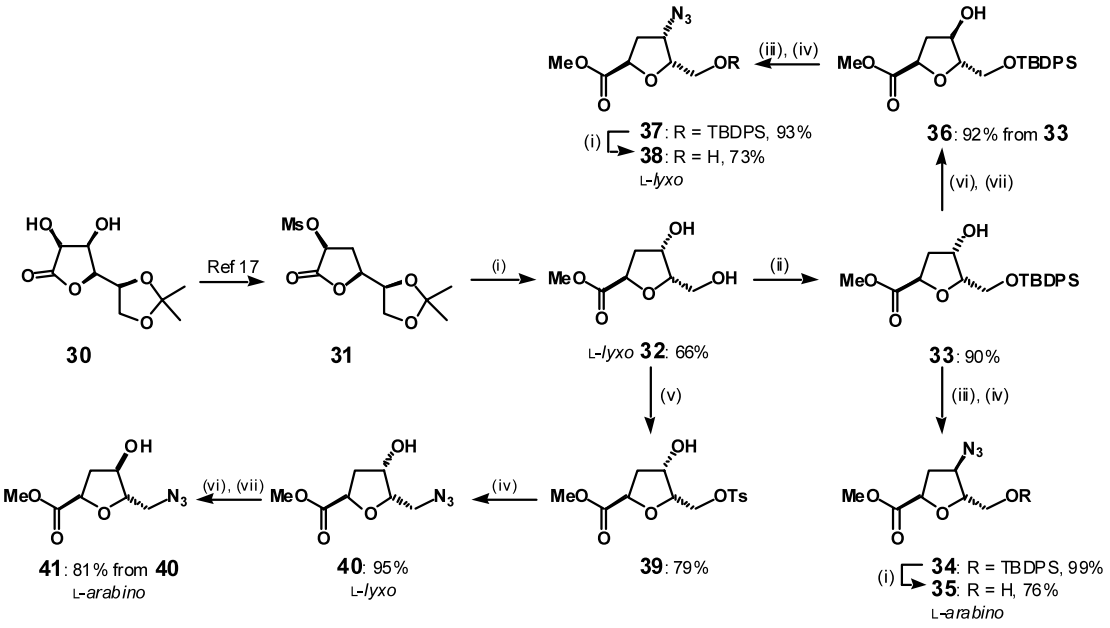
3.1. D-*xylo* γ-Azido ester 27 and D-*ribo* δ-azido ester 29

The D-*ribo* diol **21** was subsequently synthesised via a shorter route in which C-3 deoxygenation *preceded* formation of the THF ring (Scheme 3). The D-*arabino* mesylate **23** {mp 142–144°C (MeOH), lit.[17] 142–143.5°C (MeOH); $[\alpha]_D^{23}$ −25.6 (*c* 0.9), lit.[17] $[\alpha]_D^{23}$ −23 (*c* 0.86)} was prepared from the kinetic monoacetonide **22** of D-mannono-1,4-lactone[18] via a modification of the procedure of Chittenden.[17] Treatment of **23** with an acidic methanol solution afforded the D-*ribo* THF carboxylate **21** in 78% yield. A similar approach to the synthesis of the carboxylic acid corresponding to **21** has been described already by Pedersen in which **23** is generated instead from D-glucono-1,5-lactone.[12b] Although the efficiency of the route from D-mannolactone does not match Pedersen's methodology, the ready availability of L-mannono-1,4-lactone makes the present route equally applicable to the synthesis of the enantiomeric L-*ribo* carboxylate.

Introduction of nitrogen at the C-4 position of the D-*ribo* diol **21** followed a similar protocol to that described above for the D-*xylo* diol **13**. In this instance, use of the more bulky *tert*-butyldiphenylsilyl ether protecting group avoided problems of deprotection during the azide displacement step. Accordingly **21** was converted to the monosilylated product **24** in 84% yield {mp 62–64°C; $[\alpha]_D^{24}$ +24.9 (*c* 1.1)}. Esterification of **24** with methanesulfonyl chloride afforded the mesylate **25** {100%; oil; $[\alpha]_D^{24}$ +31.6 (*c*, 1.0)} which was converted to the D-*xylo* γ-azido ester **26** by the addition of sodium azide {70%; oil; $[\alpha]_D^{24}$ −18.2 (*c*, 1.2)}. Treatment of **26** with TBAF in THF to remove the 6-*O*-TBDPS group led to partial hydrolysis of the ester functionality. By stirring the mixture of crude cleavage products with a methanolic solution of HCl, the required unprotected γ-azido ester product **27**[19] was isolated in good yield



Scheme 3. *Reagents and conditions*: (i) HCl, MeOH; (ii) TBDPSCl, imidazole, DMF; (iii) MsCl, DMAP, pyridine; (iv) NaN_3, DMF; (v) TsCl, pyridine.



Scheme 4. *Reagents and conditions*: (i) HCl, MeOH; (ii) TBDPSCl, imidazole, DMF; (iii) MsCl, DMAP, pyridine; (iv) NaN_3, DMF; (v) TsCl, pyridine; (vi) Tf_2O, pyridine, DCM; (vii) CsO_2CCF_3, butanone.

after chromatography (77%). The D-*ribo* δ-azido ester **29**[20] was generated in 72% yield over two steps from the diol **21** via regioselective esterification with *p*-toluenesulfonyl chloride and subsequent treatment of the monosulfonate ester product **28** {mp 73–75°C; $[\alpha]_D^{24}$ +38.2 (*c* 1.0)} with sodium azide.

3.2. L-*lyxo* and L-*arabino* γ-azido esters 38 and 35, and L-*lyxo* and L-*arabino* δ-azido esters 40 and 41

Synthesis of L-*arabino* γ-azido ester **35** and L-*lyxo* δ-azido ester **40** followed an analogous protocol to that given in Scheme 3, employing the L-*xylo* mesylate **31** {mp 115–116°C (MeOH), lit.[17] 114–115°C (MeOH); $[\alpha]_D^{22}$ −9.2 (*c*, 0.5), lit.[17] $[\alpha]_D^{20}$ −9 (*c*, 1.6)}, available from the monoacetonide **30** of L-gulono-1,4-lactone by the methodology of Chittenden[17] (Scheme 4). Acidic methanolysis of **31** formed the L-*lyxo* THF-2-carboxylate **32** in 66% yield {oil; $[\alpha]_D^{23}$ +35.8 (*c* 1.1 in MeOH)} and treatment with *tert*-butyldiphenylsilyl chloride and imidazole gave the corresponding 6-*O*-silyl derivative **33** {90%; mp 49–50°C; $[\alpha]_D^{25}$ +11.9 (*c* 1.0)}. Mesylation followed by azide displacement introduced the required C-4 azido group with inversion of configuration, affording the L-*arabino* γ-azido ester **34** in 99% yield from **33** {oil; $[\alpha]_D^{26}$ −20.3 (*c* 1.2)}. Acid-catalysed cleavage of the TBDPS protection gave the 6-hydroxy L-*arabino* compound **35** in 76% yield.[21] The L-*lyxo* δ-azido ester **40**[22] was obtained from the L-*lyxo* diol **32** in 75% overall yield via the 6-*O*-tosylate **39** {mp 85–87°C (diethyl ether); $[\alpha]_D^{22}$ +20.4 (*c* 1.1)}.

Synthesis of the L-*lyxo* γ-azido ester **37** and L-*arabino* δ-azido ester **38** was achieved by manipulation of the C-4 configuration (Scheme 4). Conversion of the L-*lyxo* silyl ether **33** to the L-*lyxo* γ-azido ester **38** demanded introduction of a C-4 azido group with overall retention of configuration. Esterification of the C-4 hydroxyl group of **33** with triflic anhydride and displacement with caesium trifluoroacetate[23] gave the inverted alcohol **36** in 92% yield {oil; $[\alpha]_D^{23}$ −27.7 (*c* 1.0)}. Treatment of the corresponding 4-*O*-mesylate derivative with sodium azide generated the γ-azido ester **37** with the required L-*lyxo* stereochemistry in 93% yield from **36** {oil; $[\alpha]_D^{26}$ +24.3 (*c*, 1.1)}. Acidic methanolysis of **37** gave the corresponding 6-hydroxy building block **38** (73%).[24] Treatment of the 4-*O*-trifluoromethanesulfonyl derivative of the L-*lyxo* δ-azido ester **40** with caesium trifluoroacetate gave the C-4 epimeric L-*arabino* δ-azido ester **41** in 81% overall yield.[25]

4. Summary

This paper has described routes to protected forms of all diastereomeric methyl 4-amino and 6-amino-2,5-anhydro-3-deoxy-hexonates starting from either *gulono*- or *mannono*-1,4-lactones. Since both enantiomers of these starting materials are readily available, this work demonstrates the formal synthesis of *all* eight stereoisomers of both the 4-amino- and 6-amino-THF-2-carboxylate scaffolds. These THF γ- and δ-azido esters have been investigated as building blocks for THF-templated carbopeptoids up to the octamer level. Results of conformational studies on these molecules will be reported elsewhere.

Acknowledgements

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14. All optical rotations were recorded in $CHCl_3$ unless otherwise stated. All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100.6 MHz, respectively, unless otherwise stated; coupling constants (J) are quoted in Hz. Satisfactory elemental analysis or HRMS data has been obtained for all compounds.
15. **D-*ribo* γ-Azido ester 17**: oil. $[\alpha]_D^{26}$ +21.0 (c, 0.9). δ_H: 2.40 (1H, ddd, $J_{3',2}$ 7.6, $J_{3',3}$ 13.3, $J_{3',4}$ 6.2, H-3′), 2.45 (1H, app-dt, $J_{3,3'}$ 13.3, J 6.6, H-3), 3.62 (1H, dd, $J_{6,5}$ 2.6, $J_{6,6'}$ 12.5, H-6), 3.80 (3H, s, $COOCH_3$), 3.93 (1H, dd, $J_{6',5}$ 2.7, $J_{6',6}$ 12.5, H-6′), 4.04 (1H, app-quintet, J 2.5, H-5), 4.18 (1H, app-q, J 5.9, H-4), 4.66 (1H, dd, $J_{2,3}$ 6.5, $J_{2,3'}$ 7.6, H-2). δ_C: ($CDCl_3$, 50.3 MHz): 36.5 (CH_2, C-3), 52.6 (CH_3, $COOCH_3$), 60.6 (CH, C-4), 62.0 (CH_2, C-6), 75.8, 85.4 (2×CH, C-2, C-5), 173.9 (C, C-1).
16. **D-*xylo* δ-Azido ester 19**: oil. $[\alpha]_D^{23}$ −40.2 (c 1.4). δ_H: 2.23 (1H, ddd, $J_{3',2}$ 2.3, $J_{3',3}$ 14.1, $J_{3',4}$ 1.1, H-3′), 2.49 (1H, ddd, $J_{3,2}$ 9.6, $J_{3,3'}$ 14.1, $J_{3,4}$ 4.8, H-3), 3.62 (2H, m, H-6, H-6′), 3.80 (3H, s, $COOCH_3$), 4.04 (1H, app-dt, $J_{5,4}$ 3.3, J 6.3, H-5), 4.35 (1H, br-app-t, J 3.7, H-4), 4.58 (1H, dd, $J_{2,3}$ 9.7, $J_{2,3'}$ 2.3, H-2). δ_C: 39.5 (CH_2, C-3), 50.9 (CH_2, C-6), 53.2 (CH_3, $COOCH_3$), 72.3, 76.5, 83.8 (3×CH, C-2, C-4, C-5), 175.4 (C, C-1).
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19. **D-*xylo* γ-Azido ester 27**: oil. $[\alpha]_D^{25}$ −92.0 (c, 1.7). δ_H: 2.38 (1H, ddd, $J_{3,3'}$ 13.5, $J_{3,2}$ 6.1, $J_{3,4}$ 4.8, H-3), 2.63 (1H, ddd, $J_{3',3}$ 13.5, $J_{3',2}$ 8.8, $J_{3',4}$ 6.8, H-3′), 2.86 (1H, app-t, J 6.2, O*H*), 3.78 (3H, s, $COOCH_3$), 3.82 (2H, app-t, J 5.4, H-6, H-6′), 4.15 (1H, dd, $J_{5,4}$ 10.6, J 5.4, H-5), 4.22–4.27 (1H, m, H-4), 4.56 (1H, dd, $J_{2,3'}$ 8.8, $J_{2,3}$ 6.1, H-2). δ_C: 35.7 (CH_2, C-3), 52.6 (CH_3, $COOCH_3$), 61.0 (CH, C-4), 61.3 (CH_2, C-6), 75.3 (CH, C-2), 82.0 (CH, C-5), 172.9 (C, C-1).
20. **D-*ribo* δ-Azido ester 29**: oil. $[\alpha]_D^{22}$ +75.9 (c, 1.0). δ_H: 2.24–2.28 (2H, m, H-3, H-3′), 3.40 (1H, dd, $J_{6,6'}$ 12.9, $J_{6,5}$ 5.1, H-6), 3.45 (1H, dd, $J_{6',6}$ 12.9, $J_{6',5}$ 5.5, H-6′), 3.76 (3H, s, $COOCH_3$), 4.04 (app-dt, 1H, J 3.1, J 5.3, H-5), 4.33 (1H, m, H-4), 4.69 (1H, app-t, J 7.8, H-2). δ_C: 38.6 (CH_2, C-3), 52.4 (CH_3, $COOCH_3$), 52.6 (CH_2, C-6), 73.2 (CH, C-4), 76.5 (CH, C-2), 85.7 (CH, C-5), 172.5 (C, C-1).
21. **L-*arabino* γ-Azido ester 35**: oil. $[\alpha]_D^{25}$ −106.4 (c, 1.0). δ_H: 2.24 (1H, app-dt, $J_{3,3'}$ 13.4, J 5.2, H-3), 2.61 (1H, ddd, $J_{3',3}$ 13.4, $J_{3',2}$ 8.4, $J_{3',4}$ 7.6, H-3′), 3.66 (1H, d, $J_{6,6'}$ 12.2, H-6), 3.78 (3H, s, $COOCH_3$), 3.84 (1H, dd, $J_{6',6}$ 12.2, $J_{6',5}$ 3.2, H-6′), 4.06 (1H, dt, $J_{5,4}$ 5.6, $J_{5,6'}$ 3.2, H-5), 4.12 (1H, app-dt, $J_{4,3'}$ 7.6, J 5.6, H-4), 4.64 (1H, dd, $J_{2,3'}$ 8.4, $J_{2,3}$ 5.2, H-2). δ_C: 35.9 (CH_2, C-3), 52.4 (CH_3, $COOCH_3$), 60.4 (CH, C-4), 61.9 (CH_2, C-6), 76.2 (CH, C-2), 84.3 (CH, C-5), 172.4 (C, C-1).
22. **L-*lyxo* δ-Azido ester 40**: oil. $[\alpha]_D^{22}$ +47.9 (c, 1.3). δ_H: 2.27 (1H, ddd, $J_{3,3'}$ 13.6, $J_{3,2}$ 7.8, $J_{3,4}$ 2.0, H-3), 2.37 (1H, ddd, $J_{3',3}$ 13.6, $J_{3',2}$ 7.8, $J_{3',4}$ 2.0, H-3′), 3.57 (1H, dd, $J_{6,6'}$ 12.4, $J_{6,5}$ 5.8, H-6), 3.62 (1H, dd, $J_{6',6}$ 12.4, $J_{6',5}$ 6.6, H-6′), 3.76 (3H, s, $COOCH_3$), 4.21 (1H, ddd, $J_{5,6'}$ 6.8, $J_{5,6}$ 5.8, $J_{5,4}$ 4.0, H-5), 4.52 (1H, m, H-4), 4.75 (1H, app-t, J 3.9, H-2). δ_C: 39.7 (CH_2, C-3), 49.7 (CH_2, C-6), 52.3 (CH_3, $COOCH_3$), 71.9 (CH, C-4), 75.6 (CH, C-2), 81.2 (CH, C-5), 173.2 (C, C-1).
23. (a) Kruizinga, W. H.; Strijtveen, B.; Kellog, R. M. *J. Org. Chem*. **1981**, *46*, 4321–4323; (b) Bell, A. A.; Pickering, L.; Finn, M.; de la Fuente, C.; Krulle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett* **1997**, 1077–1078.
24. **L-*lyxo* γ-Azido ester 38**: oil. $[\alpha]_D^{25}$ +57.4 (c, 0.96). δ_H: 2.30 (1H, s, O*H*), 2.39 (1H, ddd, $J_{3,3'}$ 13.8, $J_{3,2}$ 7.6, $J_{3,4}$ 6.0, H-3), 2.49 (1H, ddd, $J_{3',3}$ 13.8, $J_{3',2}$ 7.6, $J_{3',4}$ 2.8, H-3′), 3.76 (3H, s, $COOCH_3$), 3.80 (1H, dd, $J_{6,6'}$ 11.4, $J_{6,5}$ 4.8, H-6), 3.87 (1H, dd, $J_{6',6}$ 11.4, $J_{6',5}$ 5.4, H-6′), 4.22–4.29 (2H, m, H-4, H-5), 4.68 (1H, app-t, J 7.6, H-2). δ_C: 36.2 (CH_2, C-3), 52.3 (CH_3, $COOCH_3$), 61.4 (CH_2, C-6), 62.0 (CH, C-4), 75.4 (CH, C-2), 82.2 (CH, C-5), 172.7 (C, C-1).
25. **L-*arabino* δ-Azido ester 41**: oil. $[\alpha]_D^{23}$ −104.0 (c, 0.9). δ_H: 2.18 (1H, app-dt, $J_{3,3'}$ 14.0, J 2.8, H-3), 2.50 (1H, ddd, $J_{3',3}$ 14.0, $J_{3',2}$ 8.8, $J_{3',4}$ 6.2, H-3′), 2.98 (1H, m, O*H*), 3.31 (1H, dd, $J_{6,6'}$ 13.0, $J_{6,5}$ 4.2, H-6), 3.48 (1H, dd, $J_{6',6}$ 13.0, $J_{6',5}$ 4.2, H-6′), 3.78 (3H, s, $COOCH_3$), 4.26–4.31 (2H, m, H-4, H-5), 4.69 (1H, dd, $J_{2,3'}$ 8.8, $J_{2,3}$ 2.8, H-2). δ_C: 38.7 (CH_2, C-3), 52.5 (CH_2, CH_3, C-6, $COOCH_3$), 73.7, 86.5 (2×CH, C-4, C-5), 76.9 (CH, C-2), 174.4 (C, C-1).