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# Asymmetric synthesis of (5*S*)-4-deoxy-5-*C*-(4-nitrophenyl)-L-*threo*-pentose and (5*R*)-5-*C*-(4-nitrophenyl)-L-arabinose

Madeleine Helliwell,[a] Iain M. Phillips,[b] Robin G. Pritchard[b] and Richard J. Stoodley[b,*]

[a]*Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*
[b]*Department of Chemistry, UMIST, PO Box 88, Manchester M60 1QD, UK*

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**Abstract**

In the presence of $Eu(fod)_3$, (1*E*)-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-diene and its (3*Z*)-4-*O*-acetyl derivative undergo *Re*-face and *endo* selective hetero Diels–Alder reactions with 4-nitrobenzaldehyde, 5-nitrofuran-2-carbaldehyde and 5-nitrothiophene-2-carbaldehyde. The cycloadducts are converted into the title compounds, early examples of 'free' 5-*C*-arylpentopyranoses. 

*Keywords:* asymmetric synthesis; carbohydrates; Diels–Alder reactions; oxygen heterocycles.

The discovery that saccharide structures play important roles in intercellular recognition and physiological regulation processes has provided a stimulus for the development of carbohydrate-related therapeutic agents.[1] However, because of their hydrophilic nature, carbohydrates usually bind weakly to their receptors, dissociation constants often being in the millimolar range.[1] Attracted by the idea of introducing hydrophobic domains into sugars and assessing the consequences of such structural changes on chemical, physical and biological properties, we have undertaken the synthesis of 5-*C*-arylpentopyranoses of type **1** and their derivatives. Such hybrid structures, which retain the stereochemical complexity of hexopyranoses, are capable of virtually limitless permutations. Thus, the aryl group can be designed to be monocyclic/polycyclic, carbocyclic/heterocyclic, electron-rich/electron-poor, neutral/charged, inert/reactive, etc.

A few stereodefined *O*-substituted 5-*C*-arylpentopyranose derivatives have been described in the literature. They have been prepared by manipulation of D-glucose[2–8] and D-galactose,[9] by cycloaddition reactions of benzaldehyde/furfural and menthol-derived siloxy dienes,[10] and by enzymic kinetic resolutions of racemic glycals (obtained by cyclocondensation reactions of benzaldehyde and siloxy dienes).[11] Seeking a synthesis that would permit extensive aryl-group variation coupled with multiple but controllable stereochemical options, we have pursued the cycloaddition approach pioneered by

* Corresponding author. E-mail: richard.stoodley@umist.ac.uk

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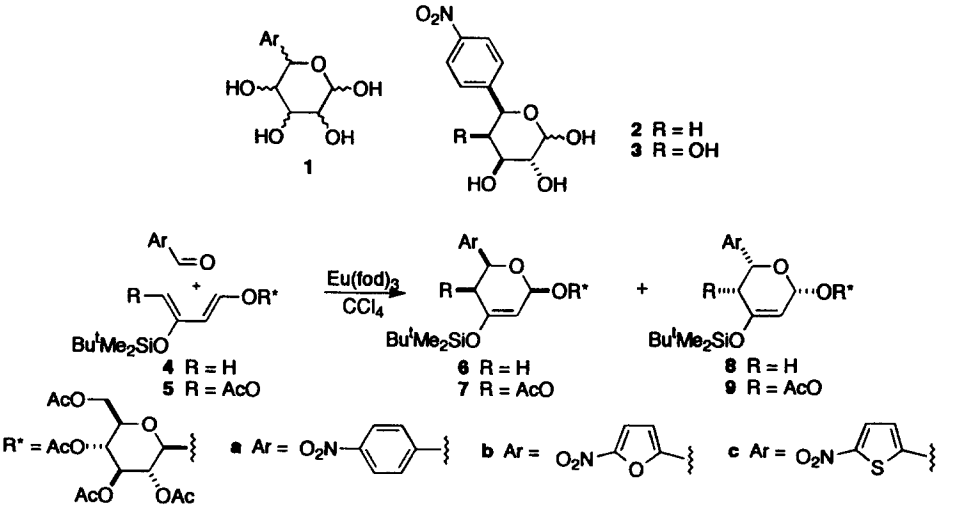
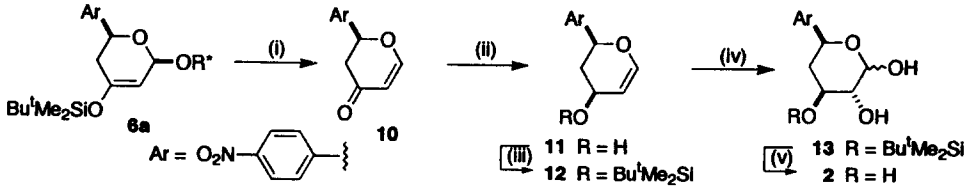
Danishefsky. In this letter, we describe the synthesis of compounds **2** and **3**, early examples of 'free' 5-*C*-arylpentopyranoses, and we compare their anomeric equilibria with those of D-fucose, D-galactose and L-arabinose.

Earlier, as outlined in Scheme 1, we had shown that the D-glucose-derived diene **4** underwent a hetero Diels–Alder reaction with 4-nitrobenzaldehyde [in $CCl_4$ containing 2 mol% $Eu(fod)_3$][12] to give mainly a 91:9 mixture of the cycloadducts **6a** and **8a**, from which the major cycloadduct **6a** was isolated by crystallisation in 80% yield.[13] We hoped that, by using other aromatic aldehydes and the diene **5**,[14] it would be possible to derive a series of cycloadducts of type **7**, which would serve as precursors of our targets. Our initial objective, however, was to establish a satisfactory route to compound **2** from the readily available cycloadduct **6a**.




Scheme 1.

The route devised is shown in Scheme 2. Thus, treatment of compound **6a** with trifluoroacetic acid gave a 50:50 mixture of the dihydropyranone **10** and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose; a simple work-up[15] and crystallisation afforded compound **10**,[13] mp 136–138°C (lit., 139–141°C) in 81% yield with an ee of 98%.[16] As noted by Danishefsky using related systems,[10] Luche reduction[17] proceeded with excellent regio- and stereo-selectivity to give the glycal **11**,[18] mp 108–110°C, $[\alpha]_D$ –93 (*c* 0.11, $CH_2Cl_2$), in 80% yield after crystallisation with an ee of >99%.[16] *tert*-Butyldimethylsilylation[19] gave the ether **12**[18] (93% yield), mp 56–58°C, $[\alpha]_D$ –48 (*c* 0.38, $CH_2Cl_2$), which underwent dihydroxylation[20] to give the diol **13**,[18] mp 123–128°C, $[\alpha]_D$ +41 (*c* 0.27, $CH_2Cl_2$), in 62% yield after crystallisation. Removal of the silyl protecting group using Fleet's conditions[21] provided (5*S*)-4-deoxy-5-*C*-(4-nitrophenyl)-L-*threo*-pentose **2**,[18] mp 119–122°C, $[\alpha]_D$ –20 (*c* 0.06, $H_2O$),[22] in 64% yield after crystallisation.




Scheme 2. *Reagents and conditions*: (i) $CF_3CO_2H$, $CH_2Cl_2$, 0.5 h; (ii) $NaBH_4$, $CeCl_3$, MeOH–EtOH, –78°C (2 h)→20°C (4 h); (iii) $Bu^tMe_2SiOTf$, $Et_3N$, $CH_2Cl_2$, 2 h; (iv) $OsO_4$ (0.3 mol%), $Ba(ClO_3)_2 \cdot H_2O$, THF, $H_2O$, 6 h; (v) Amberlite IR-120 ($H^+$), dioxan–$H_2O$, 70°C, 4 h

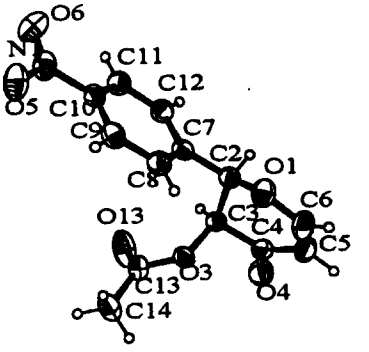
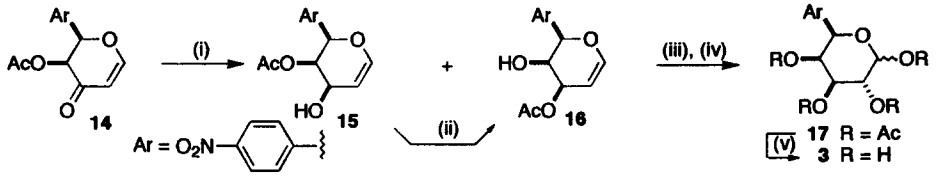


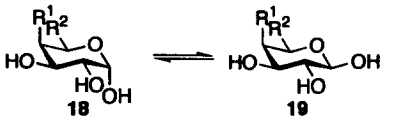

Figure 1. Molecular structure of compound **14**

Attention next focused on effecting the hetero Diels–Alder reaction of 4-nitrobenzaldehyde with the diene **5**.[14,23] Although the reaction was much slower than that involving the diene **4**, it proceeded [in $CCl_4$ containing 25 mol% of Eu(fod)$_3$] to give an 87:13 mixture of cycloadducts, presumed to possess the stereostructures **7a** and **9a**. After two crystallisations, the major cycloadduct **7a**,[18] mp 176–180°C (decomp.), $[\alpha]_D$ −123 (*c* 0.35, $CH_2Cl_2$), was isolated in 45% yield. It was readily transformed into the dihydropyranone **14**[18] (84% yield after crystallisation), mp 154–155°C, $[\alpha]_D$ −45 (*c* 0.33, $CH_2Cl_2$), by the action of trifluoroacetic acid. The structure and absolute configuration of compound **14** (see Fig. 1) was established by X-ray crystallography.[24] Luche reduction of the dihydropyranone **14** afforded a mixture of the expected alcohol **15** and its regioisomer **16**, which was converted into compound **16**[18] (76% yield after crystallisation), mp 145–146°C, $[\alpha]_D$ −13 (*c* 0.42, $CH_2Cl_2$), on treatment with triethylamine in dichloromethane (Scheme 3). Dihydroxylation followed by acetylation gave the tetraacetate **17**,[18] $[\alpha]_D$ +28 (*c* 0.23, $CH_2Cl_2$), in 75% yield. In the presence of triethylamine and methanol, the tetraacetate **17** was transformed into (5*R*)-5-*C*-(4-nitrophenyl)-L-arabinose **3**.




Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, $CeCl_3$, MeOH–EtOH, −78°C (2 h)→20°C (2 h); (ii) $Et_3N$, $CH_2Cl_2$, 2 h; (iii) $OsO_4$ (10 mol%), $Ba(ClO_3)_2 \cdot H_2O$, THF, $H_2O$, 48 h; (iv) $Ac_2O$, TfOH (cat.), 15 h; (v) MeOH, $Et_3N$, 15 h

The anomeric equilibria of compounds **2** and **3** in deuterium oxide were determined using 400 MHz $^1$H NMR spectroscopy. Thus, the ratio of the α- and β-anomers was shown to be 30:70 for compound **2** and 35:65 for compound **3**. In each case, the anomers adopted the expected chair conformations, i.e. **18a** and **18b** for the α-anomers and **19a** and **19b** for the β-anomers.[25] The aforecited equilibria were comparable with those observed for D-fucose, D-galactose and L-arabinose which existed as 30:70 mixtures of the anomers **18c–e** and **19c–e** in deuterium oxide.[26] Clearly, the anomeric and conformational equilibria of L-arabinose are little influenced by the introduction of 4-nitrophenyl, methyl or hydroxymethyl groups at the 5-*pro-R* position.




**a** $R^1$ = H, $R^2$ = 4-$NO_2C_6H_4$
**b** $R^1$ = HO, $R^2$ = 4-$NO_2C_6H_4$
**c** $R^1$ = HO, $R^2$ = Me
**d** $R^1$ = HO, $R^2$ = $HOCH_2$
**e** $R^1$ = HO, $R^2$ = H

Having devised methodology for the synthesis of the 5-*C*-arylpentopyranoses **2** and **3**, efforts were made to extend the cycloaddition to reactive heteroaromatic aldehydes. Thus, the diene **4** underwent reaction [in $CCl_4$ containing 5 mol% $Eu(fod)_3$] with 5-nitrofuran-2-carbaldehyde and 5-nitrothiophene-2-carbaldehyde to give 90:10 mixtures of the cycloadducts **6b** and **8b** and the cycloadducts **6c** and **8c**. Compound **6b**,[18] mp 122–125°C (decomp.), $[\alpha]_D$ −25 (*c* 0.29, $CH_2Cl_2$), was isolated in 75% yield after crystallisation from the former reaction and compound **6c**,[18] mp 106–107°C (decomp.), $[\alpha]_D$ −68 (*c* 0.31, $CH_2Cl_2$), in 55% yield from the latter one. Similarly, the diene **5** afforded 90:10 mixtures of the cycloadducts **7b** and **9b** and the cycloadducts **7c** and **9c**;[27] following crystallisation, compound **7b**,[18] mp 152°C (decomp.), $[\alpha]_D$ −107 (*c* 0.15, $CH_2Cl_2$), was isolated in 80% yield and compound **7c**,[18] mp 191–192°C (decomp.), $[\alpha]_D$ −73 (*c* 0.15, $CH_2Cl_2$), in 73% yield.

The aforecited results are of interest in a number of respects. In showing that the dienes **4** and **5** display comparable *Re*-face selectivities in their $Eu(fod)_3$-catalysed cycloadditions with aromatic aldehydes, they reveal that the stereodirecting role of the sugar auxiliary is not compromised by the introduction of the terminal acetoxy group. In the case of the related menthol-derived dienes developed by Danishefsky,[10] a corresponding benzoyloxy substitution led to an erosion of facial reactivity in analogous hetero Diels–Alder reactions. As a consequence of this work, the novel glycals **11**, **12** and **16** become accessible; such compounds are expected to serve as both glycosyl donors and glycosyl acceptors in the assembly of oligosaccharide congeners using Danishefsky's technology.[28] Finally, representing early examples of 'free' 5-*C*-arylpentopyranoses, compounds **2** and **3** are of intrinsic interest.

## Acknowledgements

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12. This is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III).
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15. A dichloromethane solution of the product was washed with dilute aq. sodium hydroxide (an operation which removed the glycone from the organic phase) followed by water, dried ($MgSO_4$) and concentrated.
16. The enantiomers were separated by HPLC using a Chiralpak AD column [eluent: hexanes:propan-2-ol (90:10); flow rate 1 $cm^3$ $min^{-1}$].
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22. This represents an equilibrium value.
23. This compound was prepared from the diene **4** in improved overall yield (50% rather than 16%) by sequential reactions involving dimethyldioxirane (in $Me_2CO$-$CH_2Cl_2$), methanol, acetic anydride-pyridine (at 0°C), and *tert*-butyldimethylsilyl triflate-triethylamine (in $CH_2Cl_2$ at –20°C).
24. Crystal data for compound **14**: $C_{13}H_{11}NO_6$, $M$=277.2, orthorhombic, space group $P2_12_12_1$, $a$=10.6637(14), $b$=15.4386(10), $c$=7.8078(11) Å, $V$=1285.4(3) Å$^3$, $Z$=4, $D_c$=1.433 g cm$^{-3}$, $\mu$=0.987 mm$^{-1}$ (Cu–K$\alpha$, $\lambda$=1.54178 Å), $F$(000)=576, $T$=295(2) K. Rigaku AFC5R diffractometer, crystal size 0.30×0.15×0.15 mm, $\theta_{max}$ 77.23°, 2961 reflections measured, all unique. Structure solution by direct methods, full-matrix least-squares refinement on $F^2$ with weighting $w^{-1}=\sigma^2(F_o^2)+(0.0373P)^2+0.243P$, where $P=(F_o^2+2F_c^2)/3$, anisotropic displacement parameters, riding hydrogen atoms, methyl hydrogen atoms disordered over two semi-populated sites, $\psi$-scan absorption correction, absolute structure parameter=–0.2(3) [+1.1(3) for *ent*-**14**]. Final $Rw=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}\}=0.107$ for all data, conventional $R$=0.041 on $F$ values of 2428 reflections with $I>2\sigma(I)$, $S$=1.04 for all data and 207 parameters. Final difference map between +0.18 and –0.14 e Å$^{-3}$. Programs: Rigaku/MSC AFC and PROCESS diffractometer control and processing software, SHELX97 (G. M. Sheldrick, University of Gottingen, Germany).
25. The anomeric protons appeared as doublets ($J$ 3.5 Hz) at $\delta$ 5.38 and 5.45 for the $\alpha$-anomers **18a** and **18b** and as doublets ($J$ 8 Hz) at $\delta$ 4.75 and 4.77 for the $\beta$-anomers **19a** and **19b**.
26. The anomeric protons appeared as doublets ($J$ 3.5 Hz) at $\delta$ 5.18, 5.23 and 5.22 for the anomers **18c–e** and as doublets ($J$ 8 Hz) at $\delta$ 4.52, 4.56 and 4.50 for the anomers **19c–e**.
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