Chemoenzymatic synthesis of the carbasugars carba-β-L-galactopyranose, carba-β-L-talopyranose and carba-α-L-talopyranose from methyl benzoate†‡

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The *cis*-dihydrodiol metabolite from methyl benzoate has been used as a synthetic precursor of carba-β-L-galactopyranose, carba-β-L-talopyranose and carba-α-L-talopyranose. The structures and absolute configurations of these carbasugars were determined by a combination of NMR spectroscopy, stereochemical correlation and X-ray crystallography.

Introduction

Replacement of the ring oxygen atom in monosaccharides, with a methylene group, leads to a series of carbohydrate mimetics, originally classified as pseudosugars but are now generally referred to as carbasugars.[1] The structural similarity and increased stability of carbasugars, compared with natural sugars, and the possibility of their recognition as enzyme substrates or inhibitors, have led to extensive synthetic efforts.[1] One approach to the synthesis of carbasugars has utilized enantiopure *cis*-dihydrodiols, derived from the bacterial metabolism of the corresponding monosubstituted benzene substrate. While a wide range of *cis*-dihydrodiols (>400) have been isolated from these and other laboratories,[2a–i] to date, only a few have been employed in the synthesis of carbasugars.[3a–h] The first arene *cis*-dihydrodiols used as precursors in carbasugar synthesis were those derived from benzene (R = H) (Scheme 1).[3a–c] Unfortunately the *cis*-dihydrodiol of benzene is achiral and the synthetic routes to carbasugars generally involved a significant number of steps (12–16).

Over the past fifteen years, four other *cis*-dihydrodiols (*e.g.* from toluene,[3d] benzonitrile,[3e] iodobenzene[3f,g] and methylbenzoate [3h]) have been used in carbasugar synthesis, each being enantiopure (*e.g.* R = I), with several having the required carbon skeleton (*e.g.* R = Me, CN, CO_2Me, Scheme 1).

Following on from our earlier approaches to the synthesis of carbasugars from *cis*-dihydrodiol derivative **1** of iodobenzene, we have recently examined the potential of other monosubstituted *cis*-dihydrodiols (Scheme 2)[3g]. These include *cis*-dihydrodiols **2**, **3** and **4**, derived from benzyl alcohol, benzyl acetate and methyl benzoate, respectively. In principle, the *cis*-dihydrodiol metabolite **2** of benzyl alcohol appears to be an ideal precursor of carbasugars, since it has the carbon skeleton, including the exocyclic hydroxymethylene group. As it turned out, benzyl alcohol was found to be a very poor substrate for the soil bacterium *Pseudomonas putida* UV4 – the source of toluene dioxygenase (TDO). Competitive enzyme-catalysed oxidation of the exocyclic hydroxymethylene group, to yield benzaldehyde and benzoic acid, was found to occur in preference to the formation of the required *cis*-dihydrodiol **2** and thus it was only obtained in very low yield (4%).[4]

Biotransformations of several other substrates using *P. putida* UV4 also gave the *cis*-diol metabolite **2** as a minor product, *e.g.* toluene (≤4%), benzaldehyde (8%) and benzyl cyanide (15%).[4,5] The yield of *cis*-dihydrodiol **3** obtained using *P. putida* UV 4 and benzyl acetate as substrate was slightly higher (20%) but was accompanied by a significant degree of hydrolysis to yield benzyl alcohol. No evidence of ester hydrolysis was found by the use of a recombinant strain (*E. coli* pKST7) containing TDO; *cis*-dihydrodiol **3** was isolated in an improved yield (43%)[4] and was, therefore, deemed suitable for scale-up and further study as a potential precursor of carbasugars. However, subsequent attempts to introduce *cis*- or *trans*-diol groups, regioselectively, at the unsubstituted 5,6-double bond through osmylation or epoxidation/hydrolysis proved to be more difficult due to competing oxidation at the alternative 3,4-double bond. *cis*-Dihydroxylation occurred to a lesser degree (*ca.* 10%) and epoxidation to a greater degree (*ca.* 50%), at the 3,4-double bond, generating isomeric mixtures of oxidation products. In order to improve the regioselectivity, and consequently reduce the problem of isomer separation, we explored the possibility of regioselective chemical oxidation occurring exclusively at the 5,6-double bond in *cis*-dihydrodiol **4**.

Fungal enzyme-catalysed oxidation of methyl benzoate, and identification of the resulting microbial metabolites, have recently been studied in our laboratories.[6a,b] Monooxygenase-catalysed epoxidation occurred exclusively at the 1,2-bond of methyl benzoate (and substituted methylbenzoates), in growing cultures of the *Phellinus* family of wood-rotting fungi, to give isolable 1,2-arene oxide/oxepine metabolites. These relatively stable arene oxide/oxepines were found, in turn, to hydrolyse to *trans*-dihydrodiol metabolites of methyl benzoates under weakly basic conditions.[6a,b] These arene oxide/oxepine natural products, from methyl benzoate (and derivatives) isolated in low yields (<5%), were found

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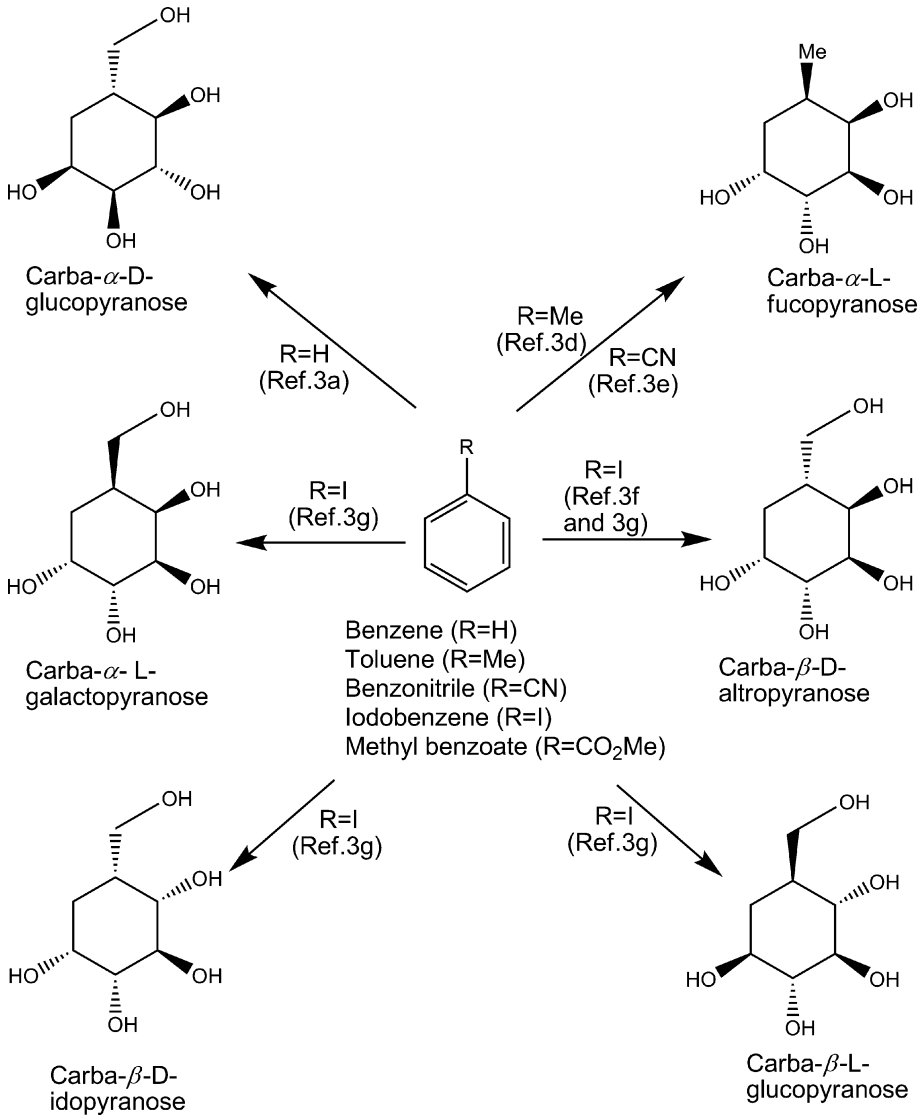
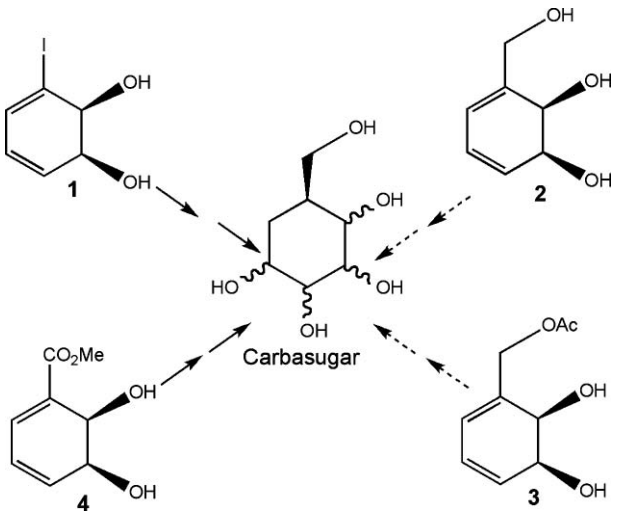


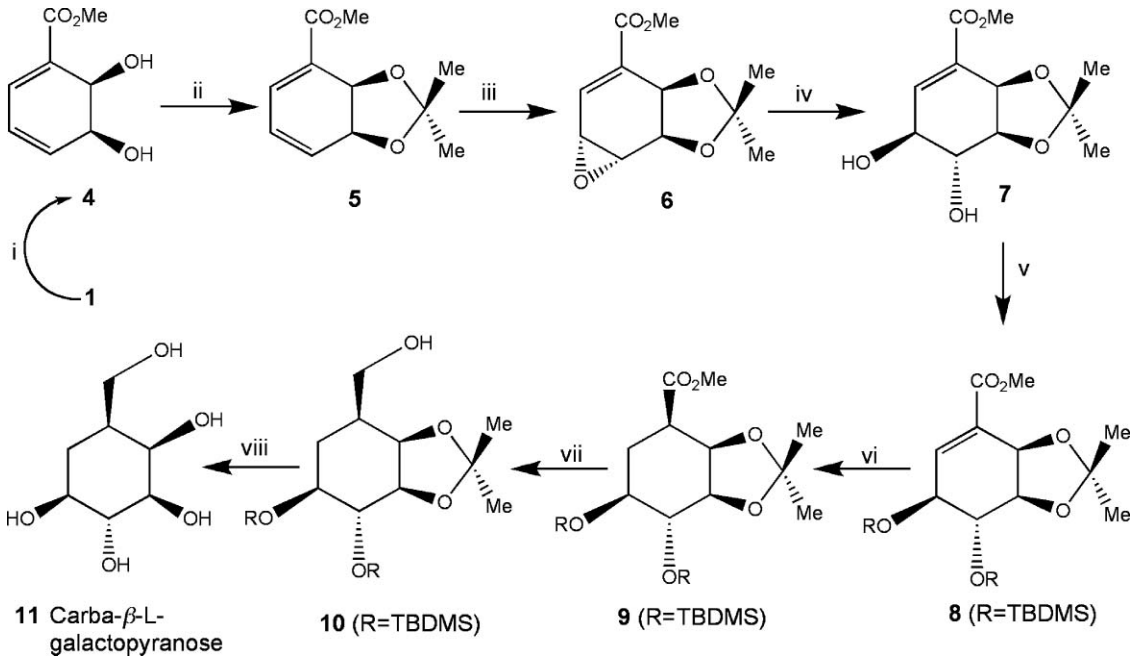
Scheme 1 Synthesis of carbasugars from benzene- and monosubstituted-benzene *cis*-dihydrodiol metabolites.



Scheme 2 Reported (**1** and **4**) and potential (**2** and **3**) benzene *cis*-dihydrodiol precursors of carbasugars.

to racemize spontaneously and were accompanied by enzymatic reduction products (benzyl alcohols). As a result, the fungal metabolites proved to be much less attractive synthetic precursors compared with the *cis*-dihydrodiol bacterial metabolites formed by dioxygenase-catalysed oxidation of methyl benzoate. Using *P. putida* UV4, *cis*-dihydroxylation was reported to occur exclusively at the 2,3-bond to give the relatively stable *cis*-dihydrodiol **4** as the sole bioproduct (53% yield),[7] in enantiopure form without any evidence of competing biotransformation pathways (*e.g.* ester hydrolysis).

Since *cis*-dihydrodiol **4** contains the required carbon skeleton of both shikimic acids and carbasugars (after reduction of the carbomethoxy group), it had earlier been used as a precursor of 6β-hydroxyshikimic acid[7] and an acetonide derivative of carba-α-L-galactopyranose.[3h] The apparent advantages of utilizing enantiopure (1*S*,2*R*)-arene *cis*-dihydrodiol **4** as a chiral precursor for the three carbasugars, carba-β-L-galactopyranose **11**, carba-β-L-talopyranose **18** and carba-α-L-talopyranose **26**, are discussed herein.



Scheme 3 *Reagents and conditions*: i CO, $Pd(OAc)_2$, $NaOAc{\cdot}3H_2O$, MeOH (62%); ii 2,2-DMP, PTSA (93%); iii MCPBA, CH_2Cl_2, (77%); iv ^{t}BuOH, H_2O, pH 8 buffer (70%); v TBDMSOTf, Et_3N, CH_2Cl_2 (82%); vi Rh–Al_2O_3, H_2, EtOH (62%); vii $LiAlH_4$, Et_2O (84%); viii MeOH, HCl (84%)

Results and discussion

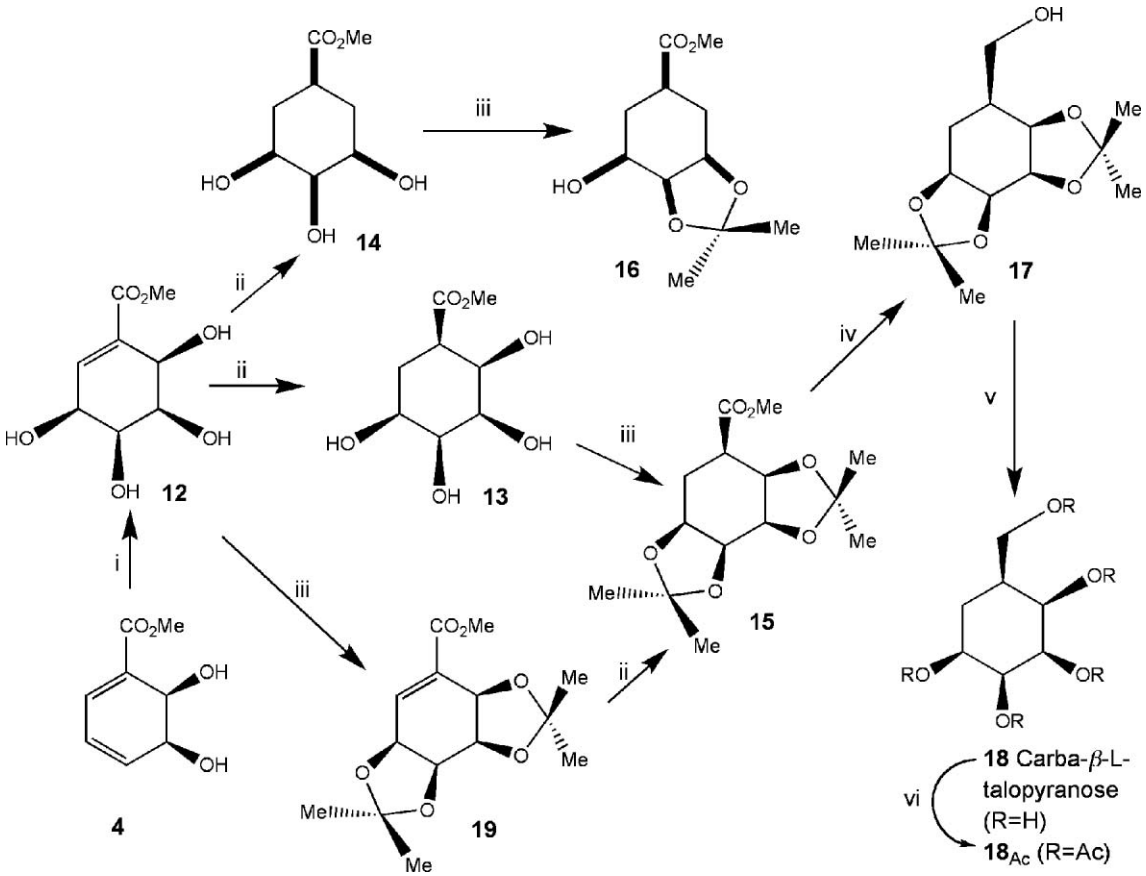
The supply of *cis*-dihydrodiol metabolite **4**, produced during the current study by TDO-catalysed biotransformations of methylbenzoate using whole cells of *P. putida* UV4 (35% yield), was supplemented by an alternative chemoenzymatic synthesis from iodobenzene *cis*-dihydrodiol **1** (Scheme 3). *cis*-Dihydrodiol **1** was available from the biotransformation (*P. putida* UV4) of iodobenzene in higher isolated yields (*ca.* 80%).[5] Carbonylation of diol **1** [$Pd(OAc)_2$, $NaOAc{\cdot}3H_2O$ in MeOH], under an atmosphere of carbon monoxide at room temperature, provided an alternative chemoenzymatic route to the (1*S*,2*R*)-*cis*-dihydrodiol **4** derivative of methylbenzoate (50% yield overall from iodobenzene).

Protection of *cis*-dihydrodiol **4** was carried out using 2,2-dimethoxypropane (DMP), in the presence of an acid catalyst (PTSA), to yield the known acetonide **5** (Scheme 3).[7] Epoxidation of compound **5** occurred in a regio- and stereo-selective manner, with the new oxygen atom being added exclusively at the 5,6 bond and *trans* to the acetonide group, to give the known epoxide **6** (77% yield).[8] Regioselective ring-opening, at the allylic carbon, was achieved using a mixture of *tert*-butanol and water buffered at pH 8, to furnish *trans*-dihydrodiol **7** (70% yield).

Protection of *trans*-diol **7** as di-TBDMS derivative **8** (82% yield), followed by hydrogenation using a Rh–Al_2O_3 catalyst, resulted in hydrogen being preferentially added from the less sterically hindered face, opposite to the acetonide group, yielding compound **9** (82% yield) after chromatography. The next step in the synthesis involved reduction of the ester group with lithium aluminium hydride to give the differentially protected form of carba-β-L-galactopyranose **10** (84% yield). Deprotection of compound **10** under acidic conditions yielded the required carbasugar **11** (84% yield) in seven steps from *cis*-dihydrodiol **4**. The reported ^{1}H- and ^{13}C-NMR spectra of carba-β-DL-galactopyranose **11** (in CD_3OD), synthesised earlier in twelve steps from *myo*-inositol,[9] was found to be similar to that of the sample of carba-β-L-galactopyranose **11** (in D_2O) derived from methyl benzoate (Scheme 3).

The chemoenzymatic synthesis of carba-β-L-talopyranose **18** from methyl benzoate *cis*-dihydrodiol **4** was achieved in five steps by two alternative routes, (Scheme 4). Stereoselective catalytic osmylation of *cis*-dihydrodiol **4** was performed by using trimethylamine-*N*-oxide dihydrate (TMANO) as the co-oxidant in CH_2Cl_2 solution.[10] Purification by chromatography (charcoal/Celite column) gave the key tetraol **12** (70% yield). Catalytic hydrogenation (5% Rh–Al_2O_3) of the alkene group in tetraol **12**, in common with hydrogen addition to compound **8** (Scheme 3), occurred stereoselectively from the less hindered face to give tetraol **13** as the major product. A competing side reaction, *i.e.* chemoselective hydrogenolysis of the pseudoaxial allylic hydroxyl group at C-6 in tetraol **12** and hydrogenation leading to the formation of achiral *meso*-triol **14**, was also observed. The mixture of tetraol **13** and triol **14** (70 : 30) was not separable by charcoal/Celite chromatography. The structure of triol **14** was, however, readily assigned in the mixture, due to its symmetry. Treatment with DMP–PTSA yielded a mixture of mono- and bis-acetonides (**16**/**15**), which was readily separated by flash column chromatography to give **15** (in 63% from tetraol **12**). A pure sample of racemic acetonide **16** was fully characterised, confirming the structure of the precursor triol **14**.

An alternative synthetic approach, to the synthesis of bis-acetonide **15**, involved protection of *cis*-tetraol **12** (as bis-acetonide **19**) followed by catalytic hydrogenation (5% Rh–Al_2O_3). Although the formation of bis-acetonide **19** was relatively slow, after leaving for 24 h the resulting mixture of mono- and bis-acetonides (*ca.* 1 : 4) was readily separated by chromatography to furnish a pure sample of bis-acetonide **19**; the minor polar mono-acetonide was recycled to give more of compound **19**, resulting in an overall



Scheme 4 *Reagents and conditions*: i OsO_4, TMANO, CH_2Cl_2 (70%); ii Rh–Al_2O_3, H_2, EtOH (**12** → **13**, >70%; **12** → **14**, <30%; **19** → **15**, 91%): compound **15**, 92%; iii 2,2′-DMP, PTSA (**13** → **15**, 59%; **12** → **16**, 25%); **12** → **19**, 80%; **15**, 59%, compound **16**, 25%: compound **19**, 80%; iv $LiAlH_4$, Et_2O (76%); v TFA, THF, H_2O (86%); vi Ac_2O, pyridine (85%).

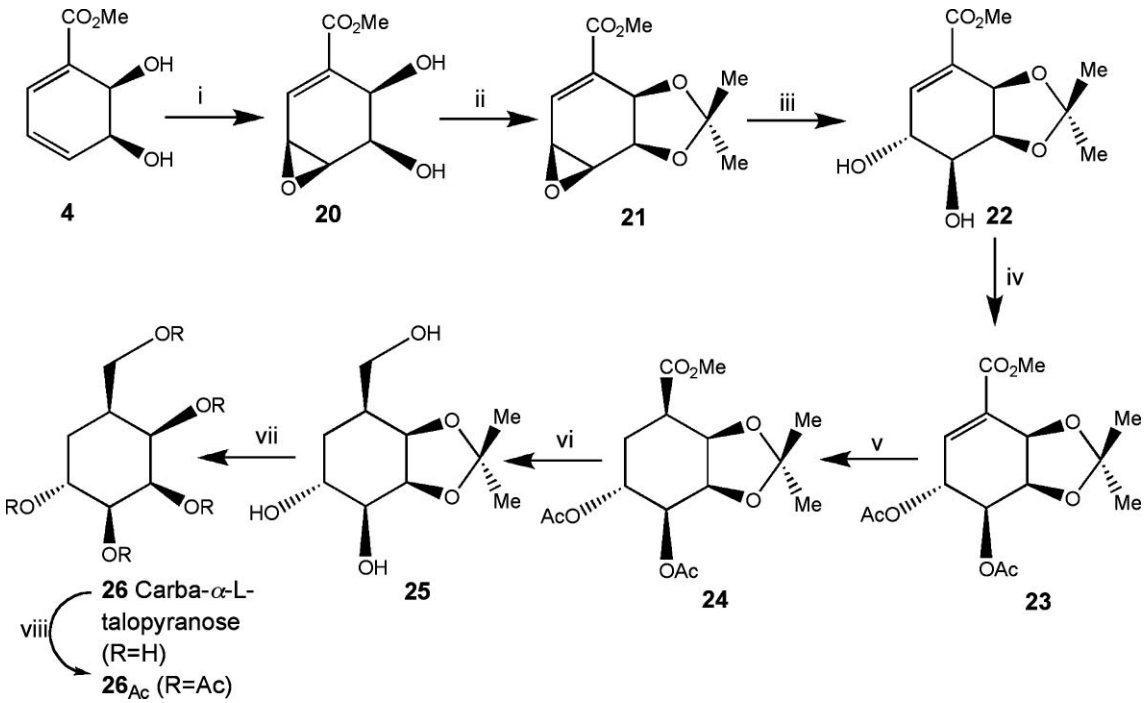
yield of *ca.* 80%. A major advantage of this approach over the hydrogenation of tetraol **12** was that the unwanted competing hydrogenolysis reaction was completely suppressed, resulting in a much higher yield (91%) of the desired compound **15**.

The final steps were similar to those used in Scheme 3 and involved reduction of ester **15** to give alcohol **17** (76% yield), followed by deprotection to afford carba-β-L-talopyranose **18** (86% yield). Further characterisation and confirmation of the structure and stereochemistry of carbasugar **18** was achieved by formation of the corresponding crystalline pentaacetate $\mathbf{18}_{Ac}$ ($[\alpha]_D$ +8.4, $CHCl_3$; 85% yield). Pentaacetate $\mathbf{18}_{Ac}$ had identical characteristics to those reported after its synthesis ($[\alpha]_D$ +5.2, $CHCl_3$) in twelve steps from D-mannose,[3b] or from the *meso-cis*-dihydrodiol of benzene ($[\alpha]_D$ –8.7, $CHCl_3$).[3c] X-Ray crystallographic analysis (Fig. 1) showed compound $\mathbf{18}_{Ac}$ to exist in a chair conformation with an equatorial CH_2OAc group and the other OAc groups adopting alternating axial and equatorial positions

The third carbasugar, carba-α-L-talopyranose **26**, was synthesised in seven steps from *cis*-dihydrodiol **4** (Scheme 5). The directing effect of the hydroxyl groups in *cis*-dihydrodiol **4** was utilized during its epoxidation using MCPBA; it resulted in the regio- and stereo-selective formation of *cis*-diol epoxide **20** (82% yield, Scheme 5). Acetonide **21** (98% yield), a stereoisomer of epoxide **6**, was similarly treated under mild alkaline conditions (*tert*-BuOH–H_2O, pH 8 buffer) (Scheme 3), to give cyclohexene *trans*-diol **22** (68% yield). Compound **22** was acetylated and the resulting diacetate **23** (98% yield) subjected to catalytic hydrogenation (H_2, 5% Rh–Al_2O_3), which occurred from the less hindered face to give the substituted cyclohexane derivative **24** (83% yield). The final steps in the synthesis of carba-α-L-talopyranose **26** were similar to those used in Schemes 3 and 4 involving ester group reduction to give triol **25** (71% yield) and deprotection to give carbasugar **26** (88% yield). The L-pentacetate derivative $\mathbf{26}_{Ac}$ ($[\alpha]_D$ –26, $CHCl_3$) was found to be spectroscopically indistinguishable from the reported sample of the opposite D-enantiomer ($[\alpha]_D$ +27.5) obtained in thirteen steps from the achiral *cis*-dihydrodiol of benzene.[3b]

Conclusion

The synthesis of three carbasugars, carba-β-L-galactopyranose **11**, carba-β-L-talopyranose **18** and carba-α-L-talopyranose **26** from (1*S*,2*R*)-*cis*-dihydrodiol metabolite **4** of methyl benzoate has been achieved in significantly fewer steps (5–7), compared with the earlier synthesis of these enantiopure carbasugars or their racemic (D/L) analogues from alternative precursors. The relative and absolute configurations have been established by a combination of X-ray crystallography, NMR spectroscopy, stereochemical correlation and comparison with literature data. The value of the single enantiomer *cis*-dihydrodiol precursor **4** in the synthesis



Scheme 5 *Reagents and conditions*: i MCPBA, CH_2Cl_2, (82%); ii 2,2-DMP, PTSA (98%); iii ^{t}BuOH, H_2O, pH 8 buffer (68%); iv Ac_2O, pyridine (98%); v Rh–Al_2O_3, H_2, EtOH (83%); vi $LiAlH_4$, Et_2O (71%); vii TFA, THF, H_2O (88%); viii Ac_2O, pyridine (82%).

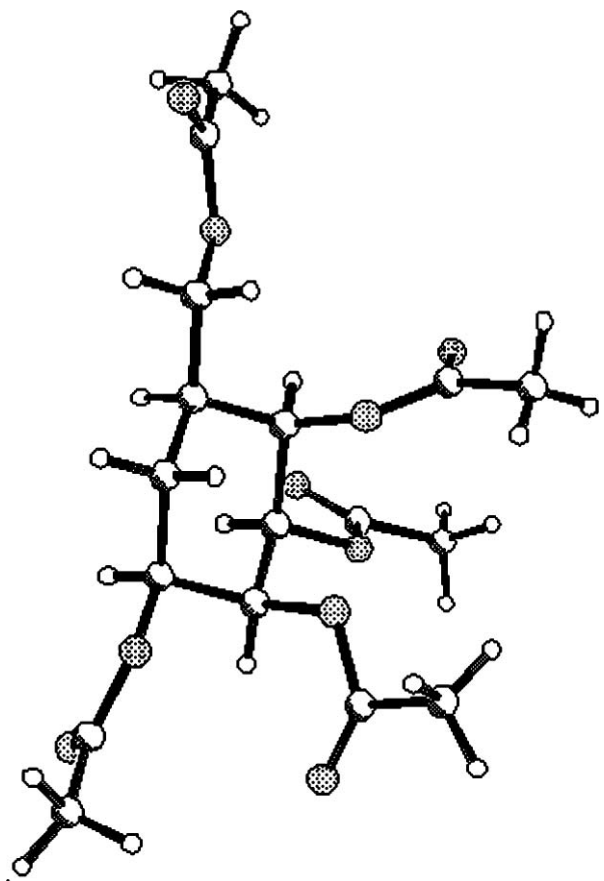


Fig. 1 X-Ray structure of pentaacetate $\mathbf{18}_{Ac}$.

of carbasugars **11**, **18** and **26** complements our earlier synthesis of four other isomeric carbasugars using *cis*-dihydrodiol **1** from iodobenzene.[3g]

Experimental

NMR (^{1}H and ^{13}C) spectra were recorded on Bruker Avance DPX-300, 3-400 and DRX-500 instruments. Coupling constants are reported in Hz and mass spectra were run at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Elemental microanalyses were carried out on a PerkinElmer 2400 CHN microanalyser. A Perkin-Elmer 341 polarimeter was used for optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{-1} deg cm^2 g^{-1}).

Flash column chromatography and preparative layer chromatography (PLC) were performed on Merck Kieselgel type 60 (250-400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel type $60F_{254}$ analytical plates were used for TLC.

cis -(1*S*,2*R*)-Dihydrodiol **4** (35% yield) was obtained by biotransformation of methyl benzoate using *P. putida* UV4 and conditions reported earlier.[5,7]

(i) Synthesis of carba-β-L-galactopyranose 11

Chemoenzymatic synthesis of methyl *cis*-(1*S*,2*R*)-1,2-dihydroxycyclohexa-3,5-diene-3-carboxylate 4. A solution of *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **1** (0.5 g, 2.1 mmol, $[\alpha]_D$ +41 (MeOH, >98% e.e.) in MeOH (50 cm^3), containing $NaOAc{\cdot}3H_2O$ (0.43 g, 3.2 mmol) and palladium(II) acetate (0.05 g), was stirred (20 h) at room temperature under carbon

monoxide (1 atm). The palladium catalyst was filtered off, the filtrate concentrated, and the residue purified by column chromatography (ethyl acetate–hexane) to yield *cis*-dihydrodiol **4** as a colourless viscous liquid (0.22 g, 62%, $[\alpha]_D$ +58, CH_2Cl_2), identical with an authentic sample obtained from the biotransformation (*P. putida* UV4) of methyl benzoate.

Methyl *cis*-(1*S*,2*R*)-1,2-isopropylidenedioxycyclohexa-3,5-diene-3-carboxylate 5. A solution of methyl (+)-*cis*-(1*S*,2*R*)-1,2-dihydroxycyclohexa-3,5-diene-3-carboxylate **4** (1.00 g, 5.88 mmol), and PTSA (0.005 g) in DMP (15 cm^3) was stirred (2 h) at room temperature. A few drops of $NaHCO_3$ solution were added to the mixture, excess DMP removed under reduced pressure, the residue treated with water (20 cm^3) and the mixture extracted with EtOAc (2 × 25 cm^3). The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the crude product purified by column chromatography (Et_2O–hexane). Acetonide **5** was obtained as a colourless oil (1.15 g, 93%); $[\alpha]_D$ +134 (*c* 0.93, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.40 (3 H, s, CMe), 1.42 (3 H, s, CMe), 3.79 (3 H, s, CO_2Me), 4.65 (1 H, d, $J_{2,1}$ 8.8, 2-H), 4.71 (1 H, dd, $J_{1,2}$ 8.8, $J_{1,6}$ 3.9, 1-H), 5.88 (1 H, dd, $J_{6,1}$ 3.9, $J_{6,5}$ 9.1, 6-H), 5.97 (1 H, d, $J_{4,5}$ 5.6, 4-H), 5.99 (1 H, d, $J_{5,4}$ 5.6, $J_{5,6}$ 9.1, 5-H). The ^{1}H-NMR spectrum was consistent with the reported data.[7]

(3*R*,4*R*,5*R*,6*R*)-3,4-Epoxy-5,6-isopropylidinedioxycyclohex-1-enecarboxylic acid methyl ester 6. MCPBA (1.30 g, 7.6 mmol) was added in small portions to a solution of (+)-acetonide **5** (1.45 g, 6.9 mmol) in CH_2Cl_2 (50 cm^3) and the mixture stirred at room temperature for 12 h. Excess MCPBA was converted into *m*-chlorobenzoic acid by stirring with a solution of $NaHSO_3$. The acid was then removed by washing the organic layer thoroughly with a saturated solution of $NaHCO_3$. The CH_2Cl_2 solution was dried ($MgSO_4$), the solvent removed under reduced pressure, and the crude product purified by column chromatography (CH_2Cl_2) to yield epoxide **6** as a colourless oil (1.20 g, 77%); $[\alpha]_D$ +94 (*c* 0.3, $CHCl_3$), (lit. $[\alpha]_D$ +101.8);[8] (Found: M^+ 226.0841. $C_{11}H_{14}O_5$ requires 226.0841); ν_{max}/cm^{-1} 1725 (C=O), 1223, 1256 (C–O); δ_H (500 MHz, $CDCl_3$) 1.40 (3 H, s, CMe), 1.43 (3 H, s, CMe), 3.45 (1 H, dd, $J_{3,2}$ 4.0, $J_{3,4}$ 1.1, 3-H), 3.57 (1 H, dd, $J_{4,3}$ 1.1, $J_{4,5}$ 3.7, 4-H), 3.81 (3 H, s, CO_2Me), 4.78 (1 H, dd, $J_{5,6}$ 7.3, $J_{5,4}$ 3.7, 5-H), 4.80 (1 H, d, $J_{6,5}$ 7.3, 6-H), 7.11 (1 H, d, $J_{2,3}$ 4.0, 2-H); *m*/*z* (EI) 226 (M^+, 3%), 211 (70).

(3*S*,4*R*,5*S*,6*R*)-3,4-Dihydroxy-5,6-isopropylidinedioxycyclohex-1-enecarboxylic acid methyl ester 7. A stirred mixture of (+)-epoxide **6** (0.20 g, 0.88 mmol), *t*-BuOH (20 cm^3) and phosphate buffer (pH 8.0, 5 cm^3) was refluxed (*ca.* 4 d) until all the epoxide had reacted. The solvent was removed under reduced pressure, saturated NaCl solution (10 cm^3) was added, the mixture extracted with EtOAc (2 × 30 cm^3), the organic extract dried ($MgSO_4$) and the EtOAc removed under reduced pressure. Purification of the crude product by PLC (60% EtOAc in hexane, R_f 0.2) yielded *trans*-diol **7** as a white solid (0.15 g, 70%); mp 130 °C (from $CHCl_3$–hexane); $[\alpha]_D$ −6.0 (*c* 0.3, $CHCl_3$); (Found: C 54.1; H 6.3. $C_{11}H_{16}O_6$ requires C 54.1; H 6.6%); ν_{max}/cm^{-1} 3425 (OH), 1724 (C=O), 1223 (C–O); δ_H (500 MHz, $CDCl_3$) 1.45 (3 H, s, CMe), 1.51 (3 H, s, CMe), 3.72 (1 H, dd, $J_{4,5}$ 8.6, $J_{4,3}$ 8.2, 4-H), 3.81 (3 H, s, CO_2Me), 4.12 (1 H, dd, $J_{5,6}$ 6.0, $J_{5,4}$ 8.6, 5-H), 4.22 (1 H, d, $J_{3,4}$ 8.2, 3-H), 4.96 (1 H, d, $J_{6,5}$ 6.0, 6-H), 6.99 (1 H, s, 2-H); *m*/*z* (EI) 244 (M^+, 15%), 229 (50).

(3*S*,4*S*,5*R*,6*R*)-5,6-Isopropylidinedioxy-3,4-di-(*tert*-butyldimethylsilanoxy)cyclohex-1-ene-carboxylic acid methyl ester 8. *tert*-Butyldimethylsilyltrifluoromethanesulfonate (0.33 g, 1.34 mmol) was added to a stirred solution of (−)-diol **7** (0.15 g, 0.61 mmol) in CH_2Cl_2 (10 cm^3) containing Et_3N (3 cm^3) at 0 °C under nitrogen. After allowing the reaction mixture to stir at room temperature for a further 30 min, it was quenched by the addition of saturated $NaHCO_3$ solution (15 cm^3). The mixture was extracted with CH_2Cl_2 (2 × 30 cm^3), the solution dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the crude product **8**. Purification by PLC (20% Et_2O in hexane, R_f 0.2) yielded compound **8** as a colourless oil (0.24 g, 82%); $[\alpha]_D$ +43 (*c* 0.7, $CHCl_3$); (Found: M^+ 472.2601. $C_{23}H_{44}O_6Si_2$ requires 472.2676); ν_{max}/cm^{-1} 1730 (C=O), 1220 (C–O); δ_H (500 MHz, $CDCl_3$) 0.09, (6 H, s $SiMe_2$), 0.12 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiBu^t$), 0.92 (9 H, s, $SiBu^t$) 1.40 (3 H, s, CMe), 1.46 (3 H, s, CMe), 3.73 (1 H, dd, $J_{4,5}$ 7.3, $J_{4,3}$ 6.8, 4-H), 3.80 (3 H, s, CO_2Me), 4.11 (1 H, dd, $J_{5,6}$ 6.4, $J_{5,4}$ 7.3, 5-H), 4.14 (1 H, $J_{3,2}$ 2.6, $J_{3,4}$ 6.8, 3-H) 4.93 (1 H, d, $J_{6,5}$ 6.4, 6-H), 6.80 (1 H, d, $J_{2,3}$ 2.6, 2-H); *m*/*z* (EI) 472 (M^+, 1%), 357 (30), 57 (100).

(1*R*,2*R*,3*R*,4*S*,5*S*)-4,5-Di(*tert*-butyldimethylsilanoxy)-2,3-isopropylidinedioxy-cyclohexane-carboxylic acid methyl ester 9. (+)-Alkene **8** (0.17 g, 0.36 mmol) was hydrogenated, in absolute EtOH (60 psi, 24 h), using 5% Rh–Al_2O_3 catalyst (0.08 g). The catalyst was filtered off, the filtrate concentrated under reduced pressure, and the crude product purified by column chromatography (30% Et_2O in hexane). The hydrogenated ester **9** was obtained as a white solid (0.14 g, 82%); mp 108–109 °C (from Et_2O–hexane); $[\alpha]_D$ +32 (*c* 0.6, $CHCl_3$); (Found: C, 58.2; H, 10.0. $C_{23}H_{46}O_6Si_2$ requires C, 58.2.9; H, 9.8%); ν_{max}/cm^{-1}1741 (C=O), 1218 (C–O); δ_H (500 MHz, $CDCl_3$) 0.075 (6 H, s, $SiMe_2$), 0.08 (6 H, s, Si Me_2), 0.89 (9 H, s, $SiBu^t$), 0.90 (9 H, s, $SiBu^t$) 1.33 (3 H, s, CMe), 1.48 (3 H, s, CMe), 1.87 (1 H, m, 6-H), 1.97 (1 H, m, 6′-H), 2.73 (1 H, m, 1-H), 3.51 (1 H, ddd, $J_{5,6'}$ 10.5, $J_{5,4}$ 6.4, $J_{5,6}$ 5.2, 5-H), 3.60 (1 H, dd, $J_{4,5}$ 6.4, $J_{4,3}$ 5.6, 4-H), 3.73 (3 H, s, CO_2Me), 4.01 (1 H, dd, $J_{3,4}$ 5.6, $J_{3,2}$ 6.0, 3-H), 4.53 (1 H, dd, $J_{2,3}$ 6.0, $J_{2,1}$ 2.7, $J_{2,6}$ 1.4, 2-H); δ_C (125 MHz, $CDCl_3$) -4.43, -4.34, -4.02 × 2, -3.89 × 2, 25.73, 26.02, 26.03, 27.41, 28.60, 40.27, 51.97, 72.79, 73.89, 77.54, 80.68; *m*/*z* (EI) 474 (M^+,1%), 359 (41), 73 (100).

[(1*S*,2*R*,3*R*,4*S*,5*S*)-4,5-bis-Di(*tert*-butyldimethylsilanoxy)-2,3-isopropylidinedioxycyclohexyl]-methanol 10. $LiAlH_4$ (0.036 g, 0.95 mmol) was added in portions to a solution of (+)-ester **9** (0.15 g, 0.32 mmol) in dry Et_2O (10 cm^3). The mixture was stirred and refluxed (16 h) under anhydrous conditions. Excess of reagent was destroyed by careful addition of moist Et_2O, brine (20 cm^3) added, and the mixture extracted with Et_2O (3 × 20 cm^3). The extract was dried ($MgSO_4$), the solvent evaporated and the crude product purified by column chromatography (30% Et_2O in hexane). Compound **10** was obtained as a gum (0.12 g, 84%); $[\alpha]_D$ −1.0 (*c* 0.9, $CHCl_3$); (Found: M^+ 446.28836. $C_{22}H_{46}O_5Si_2$ requires 446.2880); ν_{max}/cm^{-1} 1218 (C–O), 3438 (O–H); δ_H (500 MHz, $CDCl_3$) 0.076 (3 H, s, SiMe), 0.080 (3 H, s, SiMe), 0.084 (3 H, s, SiMe), 0.13 (3 H, s, SiMe), 0.89 (9 H, s, Si^tBu), 0.90 (9 H, s, Si^tBu), 1.34 (3 H, s, CMe), 1.49 (3 H, s, CMe), 1.67 (1 H, m, 1-H), 1.91 (1 H, m, 6-H), 2.13 (1 H, m, 6′-H), 3.47 (1 H, m, 7-H), 3.52 (1 H, m, 7′-H), 3.70 (1 H, ddd, $J_{4,3}$ 11.0, $J_{4,5}$ 7.5, $J_{4,2}$ 6.5, 4-H), 3.80 (1 H, ddd, $J_{5,4}$ 7.5, $J_{5,6'}$ 3.5, $J_{5,6}$ 7.2, 5-H), 3.93 (1 H, dd, $J_{3,4}$ 11.0, $J_{3,2}$ 5.5, 3-H), 4.28 (1 H, m, 2-H); δ_C (125 MHz, $CDCl_3$) -3.95, -3.76,

-3.37 × 2, -3.22 × 2, 18.63 × 2, 26.56, 26.69, 28.38, 30.92, 36.97, 65.16, 73.79, 76.34, 79.41, 82.48; *m/z* (EI) 446 (M^+, 1%), 431 (6), 331 (55), 199 (100).

Carba-β-L-galactopyranose [(1*S*,2*R*,3*R*,4*R*,5*S*)-5-hydroxymethyl cyclohexane-1,2,3,4-tetraol] 11. A solution of (–)-di-TBDMS **10** (0.076 g, 0.17 mmol) in MeOH (2 cm^3), containing few drops HCl (1 M), was stirred overnight at ambient temperature. The solvent was distilled off and the residue purified by column chromatography (1 : 1, activated charcoal : Celite, H_2O → 20% EtOH–H_2O). The fractions obtained with 20% EtOH, upon concentration, gave carbasugar **11** as a colourless oil (0.025 g, 85%); $[\alpha]_D$ −75 (*c* 0.6, $CHCl_3$); (Found 178.0841. $C_7H_{14}O_5$ requires 178.0841); ν_{max}/cm^{-1} 3359 (OH); δ_H (500 MHz, D_2O) 1.24 (1 H, m, 6-H), 1.62 (2 H, m, 5-H, 6′-H), 3.27 (1 H, dd, $J_{2,3}$ 2.9, $J_{3,4}$ 9.5, 3-H), 3.37 (3 H, m, 1-H, 2-H, 7′-H), 3.50 (1 H, dd, $J_{7,1}$ 2.9, $J_{7,7'}$ 11.0, 7-H), 3.87 (1 H, bs, 2-H); δ_C (125 MHz, $CDCl_3$) 29.17, 38.75, 62.6, 69.81, 72.16, 74.49, 75.19; *m/z* (EI) 178 (M^+, 5%), 160 (100).

(ii) Synthesis of carba-β-L-talopyranose 18

Methyl (3*S*,4*S*,5*R*,6*R*)-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 12. To a solution of (+)-diol **4** (2.50 g, 0.015 mol) and trimethylamine *N*-oxide dihydrate (3.25 g) in CH_2Cl_2 (100 cm^3) was added a catalytic quantity of OsO_4. After stirring the mixture overnight at room temperature, the solvent was distilled off and the product purified by column chromatography (1 : 1, activated charcoal : Celite, H_2O → 20% EtOH–H_2O) to yield *syn*-tetraol **12** as a colourless crystalline solid (2.10 g, 70%); mp 104–106 °C; $[\alpha]_D$ +55 (*c* 0.34, MeOH); [Found: (FAB) $(MH)^+$ 205.0712. $C_8H_{13}O_6$ requires 205.0713]; δ_H (500 MHz, D_2O) 3.84 (1 H, dd, $J_{5,6}$ 6.5, $J_{5,4}$ 4.5, 5-H), 3.87 (3 H, s, OMe), 4.21 (1 H, dd, $J_{4,5}$ 4.5, $J_{4,3}$ 6.5, 4-H), 4.49 (1 H, dd, $J_{3,2}$ 2.3, $J_{3,4}$ 6.5, 3-H), 4.63 (1 H, dd, $J_{6,5}$ 6.5, $J_{6,2}$ 1.2, 6-H), 6.92 (1 H, dd, $J_{2,3}$ 2.3, $J_{2,6}$ 1.2, 2-H); δ_C (125 MHz, D_2O) 52.69, 65.16, 67.86, 68.29, 71.44, 131.01, 141.05, 168.02 (CO_2Me); *m/z* 205 ($[MH]^+$, 45%), 112 (100).

Methyl (3*S*,4*S*,5*R*,6*R*)-3,4;5,6-diisopropylidenetetraoxycyclohexene-1-carboxylate 19. To a solution of (+)-tetraol **12** (0.204 g, 1.00 mmol) in Me_2CO (8 cm^3) was added an excess of DMP (4 cm^3) and PTSA (0.015 g). After stirring the reaction mixture overnight at room temperature, it was worked up by a procedure similar to that of compound **5**. The crude product was purified by PLC (40% EtOAc in hexane) to give the less polar, major, bis-acetonide **19** as a white solid (0.230 g, 80% after recycling); mp 86–88 °C; $[\alpha]_D$ −6.4 (*c* 0.36, $CHCl_3$); (Found: M^+, 284.1268. $C_{14}H_{20}O_6$ requires 284.1260); δ_H (500 MHz, $CDCl_3$) 1.39 (3 H, s, Me), 1.42 (3 H, s, Me), 1.45 (3 H, s, Me), 1.52 (3 H, s, Me), 3.82 (3 H, s, CO_2Me), 4.43 (2 H, m, 4-H, 5-H), 4.66 (1 H, dd, $J_{3,4}$ 2.0, $J_{3,2}$ 3.1, 3-H), 4.91 (1 H, m, 6-H), 6.84 (1 H, dd, $J_{2,3}$, 3.1 $J_{2,6}$ 0.70, 2-H); δ_C (125 MHz, $CDCl_3$) 26.29, 26.33, 26.47, 27.66, 52.28, 68.94, 72.17, 72.24, 73.14, 110.71, 111.27 × 2, 127.75, 137.83, 165.87; *m/z* (EI) 284 (M^+, 2%), 269 (M^+-CH_3, 100), 211 (31), 169 (81), 137 (72), 109 (42), 59 (58). 43(100). The more polar PLC band yielded the minor mono-acetonide, which was recycled.

Methyl (1*R*,2*R*,3*R*,4*S*,5*S*)-2,3,4,5-diisopropylidenetetraoxycyclohexane-1carboxylate 15 and (3a*R*,5*R*,7*S*,7a*S*)-methyl 7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-5-carboxylate 16. (+)-Tetraol **12** (0.50 g, 2.45 mmol) was dissolved in EtOH (20 cm^3) and subjected to catalytic hydrogenation (H_2, 5% Rh–Al_2O_3, 55 psi, 18 h). The catalyst was removed by filtration, and the filtrate concentrated under reduced pressure, to yield a mixture (3 : 1) of two hydrogenated compounds **13** (major) and **14** (minor). The mixture (0.53 g) was converted into the corresponding mixture of acetonides **15** and **16** after treatment with DMP in Me_2CO solution. These acetonides were separated by flash column chromatography (EtOAc–hexane) to gave bis-acetonide **15** as a white solid (0.44 g, 63%); mp 83–85 °C; R_f 0.25 (50% EtOAc in hexane); $[\alpha]_D$ +154 (*c* 0.44, $CHCl_3$); (Found: M^+, 286.1419. $C_{14}H_{22}O_6$ requires 286.1416); δ_H (500 MHz, $CDCl_3$) 1.33 (3 H, s, CMe), 1.36 (3 H, s, CMe), 1.49 (3 H, s, CMe), 1.54 (3 H, s, CMe), 2.13 (1 H, m, 6-H), 2.32 (2 H, m, 1-H, 6′-H), 3.73 (3 H, s, OMe), 4.07 (1 H, dd, $J_{4,5}$ 7.6, $J_{4,3}$ 3.7, 4-H), 4.37 (1H, ddd, $J_{5,6}$ 9.4, $J_{5,6'} = J_{5,4}$ 7.6, 5-H), 4.56 (1 H, dd, $J_{3,2}$ 7.1, $J_{3,4}$ 3.7, 3-H), 4.67 (1 H, ddd, $J_{2,3}$ 7.1, $J_{2,1}$ 3.6, $J_{2,6}$ 1.8, 2-H); δ_H (125 MHz, $CDCl_3$) 23.85, 24.31, 25.32, 26.14, 26.30, 41.66, 52.04, 72.77, 73.17, 73.47, 73.90, 109.44, 110.02, 171.52; *m/z* (EI) 286 (M^+, 24%), 271 (90), 171 (32), 153 (40), 139 (51), 125 (66), 111 (46), 73 (70), 59 (82), 43 (100).

Catalytic hydrogenation of (-)-*bis*-acetonide **19**, under similar conditions to those used for tetraol **12**, gave the hydrogenated product, (+)-*bis*-acetonide **15**, as the sole product (91% yield).

(3a*R*,5*R*,7*S*,7a*S*)-Methyl 7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-5-carboxylate 16. The minor acetonide **16** was isolated as a colourless oil (0.14 g, 25%); R_f 0.5, (50% EtOAc–hexane); (Found: M^+, 230.1150. $C_{11}H_{18}O_5$ requires 230.1154); δ_H (500 MHz, $CDCl_3$) 1.36 (3 H, s, CMe), 1.52 (3 H, s, CMe), 1.78 (1 H, q, $J_{4,4} = J_{4,3a} = J_{4,5}$ 8.9, 4-H ax), 1.86 (1 H, q, $J_{6,6'} = J_{6,7} = J_{6,5}$ 11.3, 6-H ax), 2.04 (2 H, m, 4-H, 6-H both eq), 2.12 (1 H, d, *J* 9.1, OH), 2.33 (1 H, m, 5-H), 3.70 (3 H, s, OMe), 3.83 (1 H, m, 7-H), 4.23 (1 H, dd, $J_{3a,4}$ 8.9, $J_{3a,7a}$ 5.7, 3a-H), 4.28 (1 H, m, 7a-H); δ_C (75 MHz, $CDCl_3$) 25.94, 27.81, 29.99, 30.36, 36.82, 52.01, 68.22, 74.02, 75.26, 109.32, 174.54; *m/z* (EI) 230 (M^+, 4%), 215 (93), 155 (38), 123 (75), 95 (96), 67 (68), 59 (83), 43 (100).

(1*S*,2*R*,3*R*,4*S*,5*S*)-2,3,4,5-Diisopropylidenetetraoxycyclohexylmethanol 17. To a solution of (+)-bis-acetonide **15** (0.2 g, 0.7 mmol), in dry Et_2O (10 cm^3), $LiAlH_4$ (0.080 g, 2.1 mmol) was added and the mixture refluxed (18 h) under anhydrous conditions. The reaction mixture was quenched with moist Et_2O, the solvent removed under reduced pressure, and the crude product crystallized from ether–hexane to afford alcohol **17** as a white crystalline solid (0.136 g, 76%); mp 90–92 °C (decomp.); $[\alpha]_D$ +117 (*c* 0.44, $CHCl_3$); (Found: C, 60.2; H, 8.4. $C_{13}H_{22}O_5$ requires C, 60.5; H, 8.6%); δ_H (500 MHz, $CDCl_3$) 1.35 (3 H, s, Me), 1.37 (3 H, s, Me), 1.51 (3 H, s, Me), 1.55 (3 H, s, Me), 1.88 (2 H, m, 6-H, 6′-H), 2.14 (1 H, m, 1-H), 3.72 (2 H, m, 7-H, 7′-H), 4.09 (1 H, dd, $J_{4,5}$ 7.4, $J_{4,3}$ 3.8, 4-H), 4.42 (1 H, ddd, $J_{5,4}$ 7.4, $J_{5,6} = J_{5,6'}$, 7.8, 5-H), 4.48 (1 H, dd, $J_{3,2}$ 7.3, $J_{3,4}$ 3.8, 3-H), 4.54 (1 H, m, 2-H); δ_C (75 MHz, $CDCl_3$) 24.13, 24.83, 25.33, 26.11, 26.31, 36.88, 64.08, 73.25, 73.29, 73.92, 74.42, 108.99, 109.72.

Carba-β-L-talopyranose [(1*S*,2*S*,3*R*,4*R*,5*S*)-5-hydroxymethyl-cyclohexane-1,2,3,4-tetraol)] 18. A solution of (+)-alcohol **17** (0.13 g, 0.5 mmol) in a mixture (2 cm^3) of TFA–THF–H_2O (0.5 : 4 : 1) was kept (2 h) at 60 °C and then allowed to stir overnight at room temperature. The solvents were removed under

reduced pressure and the crude product purified by column chromatography (1 : 1, activated charcoal : Celite, H_2O → 5% EtOH–H_2O) to give carba-β-L-talopyranose **18** as a colourless syrup; (0.080 g, 86%); $[\alpha]_D$ +3.6 (*c* 0.56, H_2O); (Found: M^+–$2H_2O$, 142.0625. $C_7H_{10}O_3$ requires 142.0629); δ_H (500 MHz, D_2O) 1.60 (2 H, m, 7-H, 7′-H), 1.70 (1 H, m, 5-H), 3.59 (2 H, m, 4-H, 6-H), 3.73 (2 H, m, 1-H, 6′-H), 4.02 (2 H, m, 2-H, 3-H); δ_C (75 MHz, D_2O) 24.38, 39.51, 62.87, 69.32, 70.06, 70.72, 74.72; *m/z* (EI) 142 (M^+–$2H_2O$, 8%), 124 (7), 116 (13), 111 (17), 100 (17), 86 (49), 72 (100), 69 (42), 57 (43) 31 (77).

Carba-β-L-talopyranose pentaacetate 18_{Ac}. (+)-Carbasugar **17** (0.030 g, 0.17 mmol) was treated with Ac_2O (0.25 cm^3) in pyridine (0.5 cm^3) and the mixture stirred overnight at room temperature. Excess pyridine was removed under reduced pressure, the residue taken up in EtOAc (15 cm^3) and the solution washed successively with 0.5 N HCl and water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield pentaacetate $\mathbf{18_{Ac}}$ as a colourless crystalline solid (0.055 g, 85%); mp 140–141 °C (EtOAc–hexane), (lit.[11] 135–138 °C; lit[3b] 139–140 °C); $[\alpha]_D$ + 8.4 (*c* 0.82, $CHCl_3$), (lit.[11] $[\alpha]_D$ +5.2; lit_{ent}[3b] −8.7); (Found: C, 52.4; H, 6.1. $C_{17}H_{24}O_{10}$ requires C, 52.6; H, 6.2%); δ_H (500 MHz, $CDCl_3$) 1.70 (1 H, ddd, $J_{6,6'}$ 12.6, $J_{6,1} = J_{6,5}$ 4.8, 6-H), 1.91 (1 H, q, $J_{6',6} = J_{6',1} = J_{6',5}$ 12.6, 6′-H), 1.99 (3 H, s, OAc), 2.02 (3 H, s, OAc), 2.04 (3 H, s, OAc), 2.09 (3 H, s, OAc), 2.13 (3 H, s, OAc), 3.94 (1 H, dd, $J_{7,7'}$ 11.0, $J_{7,1}$ 6.2, 7-H), 4.08 (1 H, dd, $J_{7',7}$ 11.0, $J_{7',1}$ 8.8, 7′-H), 4.93 (2 H, m, 4-H, 1-H), 5.41 (1 H, dd, $J_{2,1} = J_{2,3}$ 3.0, 2-H), 5.51 (1 H, t, $J_{3,4} = J_{3,2}$ 3.0, 3-H); δ_C (125 MHz, $CDCl_3$) 20.56, 20.68, 20.74, 20.79, 20.83, 23.54, 35.40, 63.03, 66.24, 68.79, 68.99, 69.01, 169.60, 169.84, 169.97, 170.09, 170.78.

Crystal data for (+)-pentaacetate 18_{Ac}. $C_{17}H_{24}O_{10}$, $M = 388.4$, monoclinic, $a = 8.860(2)$, $b = 8.897(2)$, $c = 13.022(3)$ Å, $\beta = 109.05(3)°$, $U = 970.3(4)$ Å^3, $T = 298(2)$ K, Mo-Kα radiation, $\lambda = 0.71073$ Å, space group $P2_1$ (no. 4), $Z = 2$, $F(000) = 412$, $D_x = 1.329$ g cm^{-3}, $\mu = 0.110$ mm^{-1}, Bruker SMART CCD diffractometer, ϕ/ω scans, $3.3° < 2\theta < 57.3°$, measured/independent reflections: 11 280/4312, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms were located in a difference Fourier synthesis but were included in the final refinement at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. Final $R_1 = 0.047$ for 3163 data with $F_o > 4\sigma(F_o)$, 249 parameters, $wR_2 = 0.128$ (all data), GoF = 0.97, $\Delta\rho_{min,max} = -0.19/0.18$ e Å^{-3}. CCDC 746877.

(iii) Synthesis of carba-α-L-talopyranose 26

Methyl (1a*S*,4*R*,5*R*,5a*R*)-4,5-dihydroxy-1a,4,5,5a-tetrahydro-1-benzoxirene-3-carboxylate 20. Following the procedure given for the synthesis of compound **6**, methyl benzoate (+)-*cis*-dihydrodiol **4** (2.00 g, 11.8 mmol) was treated with MCPBA (2.21 g, 13.0 mmol) in CH_2Cl_2 solution (50 cm^3). Purification of the crude product, by column chromatography (MeOH–$CHCl_3$), yielded compound **20** as an oil (1.79 g, 82%); $[\alpha]_D$ −125 (*c* 1.27, MeOH); (Found: M^+, 186.0521. $C_8H_{10}O_5$ requires 186.0528); ν_{max}/cm^{-1}(neat): 3421 (O–H), 1716 (C=O); δ_H (400 MHz, D_2O): 3.70 (2 H, m, 1a-H, 5a-H), 3.77 (3 H, s, CO_2Me), 4.08 (1 H, d $J_{4,5}$ 5.0, 4-H), 4.57 (1 H, dd, $J_{5,4}$ 5.0, $J_{5,5a}$ 2.0, 5-H), 7.28 (1 H, d, $J_{2,1a}$ 4.0, 2-H); δ_C (100 MHz, D_2O): 48.71, 52.67, 57.98, 64.30, 67.54, 135.19, 138.61, 167.20; *m/z*: 186 (M^+, 0.5%), 168 (8), 152 (33), 139 (47), 125(100).

Methyl(3a*R*,5a*S*,6a*R*,6b*S*)-2,2-dimethyl-3a,5a,6a,6b-tetrahydrooxireno[2′,3′:3,4]-benzo-[*d*][1,3]dioxole-4-carboxylate 21. (–)-Epoxide **20** (1.60 g, 8.60 mmol) on reacting with DMP–PTSA gave crude acetonide **21**. Purification by PLC (50% Et_2O in hexane, R_f 0.26) yielded acetonide **21** as a colourless oil (1.9 g, 98%); $[\alpha]_D$ −118 (*c* 0.73, $CHCl_3$); (Found: M^+, 226.0852. $C_8H_{10}O_5$ requires 226.0841); ν_{max}/cm^{-1}(neat): 1719 (C=O); δ_H (500 MHz, $CDCl_3$): 1.46 (3 H, s, CMe), 1.53 (3 H, s, CMe), 3.60 (1 H,dd, $J_{5a,5}$ 3.8, $J_{5a,6a}$ 3.4, 5a-H), 3.70 (1 H, dd, $J_{,6a,5a}$ 3.8, $J_{6a,6b}$ 2.4, 6a-H), 3.81 (3 H, s, CO_2Me), 4.46 (1H, dd, $J_{6b,6a}$ 2.4, $J_{6b,3a}$ 6.4, 6b-H), 5.04 (1H, d, $J_{3a,6b}$ 6.4, 3a-H), 7.45 (1H, d, $J_{5,5a}$ 3.8, 5-H); δ_C (125 MHz, $CDCl_3$): 25.51, 27.34, 48.98, 52.36, 56.66, 69.08, 73.01, 108.54, 132.29, 139.42, 165.38; *m/z*: 227 ([M + 1]$^+$, 7%), 211 (100).

Methyl (3a*R*,6*R*,7*S*,7a*S*)-6,7-dihydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate 22. A solution of (–)-acetonide **21** (1.85 g, 8.19 mmol), in a mixture of pH 8.0 buffer (5 cm^3) and ^{t}BuOH (20 cm^3), was gently refluxed until the reaction was complete (*ca.* 7 d). The solvent was removed *in vacuo*, saturated NaCl solution (15 cm^3) added to the concentrate, and the mixture extracted with EtOAc (3 × 20 cm^3). The extract was dried (Na_2SO_4), concentrated *in vacuo*, and the product purified by PLC (R_f 0.11, 50% ethyl acetate–hexane) to yield *trans*-diol **22** as a white crystalline solid (1.28 g, 64%); mp 145 °C (EtOAc–hexane); $[\alpha]_D$ −13 (*c* 0.95, $CHCl_3$); (Found: M–Me^+, 229.0705. $C_{10}H_{13}O_6$ requires 229.0699); ν_{max}/cm^{-1}(neat): 3364 (O–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (3 H, s, CMe), 1.41 (3 H, s, CMe), 3.59 (1 H, dd, $J_{7a,3a}$ 5.6, $J_{7a,7}$ 7.4, 7a-H), 3.81 (3 H, s, CO_2Me), 4.52 (1 H, d, $J_{3a,7a}$ 5.6, 3a-H), 4.61 (1 H, dd, $J_{7,6}$ 7.6, $J_{7,7a}$ 7.4, 7-H), 5.11 (1 H, dd, $J_{6,5}$ 1.7, $J_{6,7}$ 7.6, 6-H), 6.92 (1 H, d, $J_{5,6}$ 1.7, 5-H); δ_C (125 MHz, $CDCl_3$): 25.69, 27.14; 52.29, 68.66, 72.60, 74.29, 74.77, 110.11, 129.54, 141.42, 165.81; *m/z*: (EI) 244 (M^+, 1%), 229 (33), 139 (100).

Methyl (3a*R*,6*R*,7*S*,7a*R*)-6,7-di(acetyloxy)-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate 23. (–)-*trans*-Diol **22** (1.30 g, 5.33 mmol) on reacting with Ac_2O–pyridine yielded crude diacetate product. Purification by PLC (R_f 0.3, 50% Et_2O–hexane) afforded diacetate **23** as a colourless oil (1.63 g, 98%); $[\alpha]_D$ −118 (*c*. 0.62, $CHCl_3$); (Found: M–CH_3^+, 313.0928. $C_{14}H_{17}O_8$ requires 313.0923); ν_{max}/cm^{-1}(neat): 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (3 H, s, CMe), 1.39 (3 H, s, CMe), 2.10 (3 H, s, OAc), 2.15 (3 H, s, OAc), 3.81 (3 H, s, CO_2Me), 4.61 (1 H, d, $J_{3a,7a}$ 5.3, 3a-H), 5.10 (1 H, dd, $J_{7a,3a}$ 5.3, $J_{7a,7}$ 7.2, 7a-H), 5.16 (1 H, dd, $J_{7,6}$ 9.3, $J_{7,7a}$ 7.2, 7-H), 5.84 (1 H, dd, $J_{6,7}$ 9.3, $J_{6,5}$ 1.8, 6-H), 6.71 (1 H, d, $J_{5,6}$ 1.8, 5-H); δ_C (125 MHz, $CDCl_3$): 19.76, 19.89, 25.23, 26.45 × 2, 51.43, 66.99, 70.49, 71.64, 72.83, 109.82, 130.61, 135.55, 164.38; *m/z* (EI) 328 (M^+, 1%), 313 (47), 43 (100).

Methyl (3a*R*,4*R*,6*R*,7*S*,7a*R*)-6,7-di(acetyloxy)-2,2-dimethyl-perhydro-1,3-benzodioxole-4-carboxylate 24. Catalytic hydrogenation (H_2, 5% Rh–Al_2O_3, 35 psi, 20 h) of (–)-diacetate **23** (1.00 g, 3.05 mmol) in EtOH (30 cm^3) gave, after purification by column chromatography (MeOH–$CHCl_3$), hydrogenated triester **24** as a viscous gum (0.84 g, 83%); $[\alpha]_D$ −39 (*c* 0.51, $CHCl_3$); (Found: M^+, 330.1316. $C_{15}H_{22}O_8$ requires 330.1315); ν_{max}/cm^{-1}(neat): 1741 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (3 H, s, CMe), 1.50 (3 H, s, CMe), 1.84 (1 H, m, 5-H), 2.03 (3 H, s, OAc),

2.13 (3 H, s, OAc), 2.52 (1 H, m, 5′-H), 2.75 (1 H, m, 4-H), 3.73 (3 H, s, CO_2Me), 4.54 (1 H, dd, $J_{7a,3a}$ 7.6, $J_{7a,7}$ 2.8, 7a-H), 4.82 (1 H, ddd, $J_{3a,7a}$ 7.6, $J_{3a,4}$ 3.1, $J_{3a,7}$ 1.6, 3a-H), 5.06 (1 H, m, 7-H), 5.23 (1 H, ddd, $J_{6,7}$ 8.2, $J_{6,5'}$ 1.3, $J_{6,5}$ 1.3, 6-H); δ_C (125 MHz, $CDCl_3$): 20.94, 20.97, 23.90, 25.64, 25.70, 39.24, 51.89, 68.70, 71.55, 73.34, 74.02, 109.72, 170.33, 170.73, 171.36; *m/z* (EI) 330 (M^+, 2%), 315 (68), 43 (100).

[(1*S*,2*R*,3*S*,4*S*,5*R*)-4,5-Dihydroxy-2,3-isopropylidenedioxycyclohexyl]-methanol 25. A solution of (–)-triester **24** (0.200 g, 0.61 mmol) in dry Et_2O (30 cm^3) was treated with an excess of $LiAlH_4$ in a similar manner to compounds **9** and **15**. Purification by column chromatography (MeOH–$CHCl_3$) yielded triol **25** as a colourless gum (0.094 g, 71%); $[\alpha]_D$ −6.5 [*c* 1.3, $(CD_3)_2O$]; (Found: M^+–Me, 203.0917. $C_9H_{15}O_5$ requires 203.0919); δ_H (500 MHz, $(CD_3)_2O$) 1.26 (3 H, s, CMe), 1.36 (3 H, s, CMe), 1.45 (1 H, m, H-6), 1.8 (1H, ddd, $J_{6',6}$ 13.8, $J_{6',1} = J_{6',5}$ 8.0, 6′-H), 1.86 (1 H, m, 1-H), 3.42 (1 H, m, 7-H), 3.53 (2 H, m, 4-H, 7′-H), 4.39 (1 H, dd, $J_{3,4}$ 3.4, $J_{3,2}$ 7.6, 3-H), 4.49 (1 H, ddd, $J_{2,3}$ 7.6, *J* 2.69, *J* 1.22, 2-H); δ_C (125 MHz, $(CD_3)_2O$) 22.26, 24.21, 34.11, 34.30, 61.95, 66.55, 71.60, 72.95, 74.73, 106.59; *m/z* (EI): 203 (M^+-Me, 68%), 97 (37), 95 (50), 83 (57), 71 (49), 59 (79), 57 (69), 55 (66), 43 (100), 42 (74), 41 (80).

Carba-α-L-talopyranose[(1*R*,2*S*,3*R*,4*R*,5*S*)-5-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol] 26. (–)-Trihydroxyacetonide **25** (0.13 g, 0.6 mmol) was deprotected, following the procedure given for the removal of the acetonide group in compound **17**. Purification of the crude product by a charcoal/Celite column yielded carbasugar **26** as a gum (0.090 g, 85%); $[\alpha]_D$ +11 (*c* 1.2, MeOH); (Found: M^+, 178.0835. $C_7H_{14}O_5$ requires 178.0841); δ_H (500 MHz, D_2O) 1.57 (1 H, dt, $J_{6e,1} = J_{6e,5}$ 4.3, $J_{6e,6a}$ 14.31, 6-H), 1.88 (1 H, m, 6′-H), 2.10 (1 H, m, 5-H), 3.66 (1 H, m, 7-H), 3.76 (1 H, m, 7′-H), 3.85 (1 H, br s, 3-H), 3.90 (1 H, br s, 2-H), 4.12 (2 H, br d, *J* 7.52, 1-H, 4-H); δ_C (125 MHz, D_2O) 25.21, 38.07, 62.63, 69.29 × 2, 71.39, 74.12; *m/z* (EI) 178 (M^+, 3%), 149 (30), 71 (25), 57 (35), 44 (82), 42 (91), 41 (100).

Carba-α-L-talopyranose pentaacetate 26_{Ac}. Carba-α-L-talopyranose **26** (0.030 g, 0.17 mmol) was acetylated using Ac_2O–pyridine. Pentaacetate $\mathbf{26_{Ac}}$ was obtained as a colourless gum (0.054 g, 82%); $[\alpha]_D$ −26.0 (*c* 1.2, $CHCl_3$) (lit.[8] + 27.5, D-isomer); (Found: M^+, 388.1372. $C_{17}H_{24}O_{10}$ requires 388.1369); δ_H (500 MHz, $CDCl_3$) 1.65 (1 H, m, 6-H), 1.96 (1 H, m, 6′-H), 2.01 (3 H, s, OCOMe), 2.04 (3 H, s, OCOMe), 2.07 (6H, s, OCOMe), 2.10 (3 H, s, OCOMe), 2.42 (1 H, m, 1-H), 3.97 (1 H, m, 1-H), 4.10 (1 H, m, $J_{1B,1}$ 11.1, H-1B), 5.13 (1 H, m, H-5), 5.16 (1 H, m, H-4), 5.21 (1 H, t, *J* 3.4, H-3), 5.40 (1 H, t, *J* 3.1, H-2); δ_C (125 MHz, $CDCl_3$) 19.68, 19.71, 19.76, 19.77, 20.03, 22.95, 32.66, 61.96, 66.28, 67.35, 67.44, 67.52, 168.37, 168.47, 168.79, 168.93, 169.36; *m/z* (EI) 388 (M^+, 8%), 329 (16), 268 (23), 243 (48), 226 (39), 166 (77), 124 (80).

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