Syntheses of the D-Aldopentoses from Non-carbohydrate Sources

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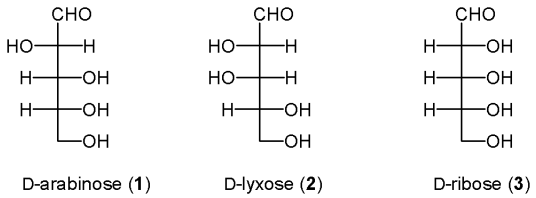
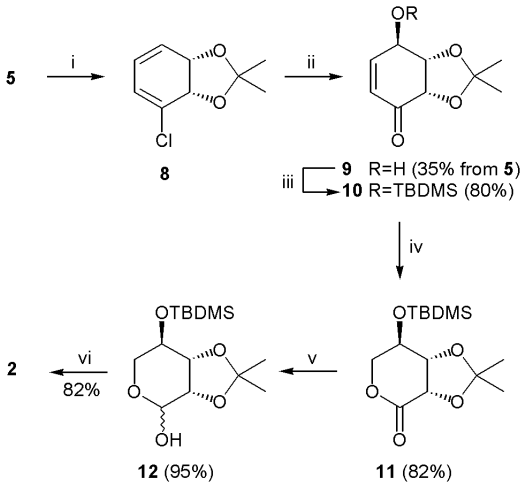
Abstract: The *cis*-1,2-dihydrocatechols **5**-**7**, which are obtained in high yield and *ca.* 99.8% ee by microbial oxidation of the corresponding aromatic compound, have been converted, *via* reaction sequences involving three distinct types of one-carbon deletion processes, into the four D-aldopentoses.

Key words: D-arabinose, 1,2-diol cleavage, *cis*-1,2-dihydrocatechol, D-lyxono-δ−lactone, D-lyxose, ozonolytic cleavage, D-ribose, radical decarboxylation, D-xylose

The D-aldopentoses **1**-**4** and their derivatives are of considerable interest as starting materials for chemical synthesis,[1] as building blocks in the construction of carbohydrate-based drugs[2] and as probes of various biochemical processes.[3] Consequently, new methods for the preparation of differentially protected and/or isotopically labelled forms of these compounds should prove valuable. The capacity to prepare such five-carbon sugars, especially ^{17}O-, ^{13}C- and/or ^{2}H-labelled variants,[4] could be greatly facilitated by using appropriate non-carbohydrate based starting materials.[4b,5] However, in contrast to the considerable effort that has been devoted to the synthesis of various pentitols[6] and the aldohexoses,[7] much of which exploits asymmetric epoxidation chemistry, examples of the preparation of the aldopentoses from non-carbohydrate sources remain rather limited.[3c,8] In an important contribution to the general area, Hudlicky *et al.*[9] have demonstrated that the enantiopure six-carbon *cis*-1,2-dihydrocatechol **5** can be converted into L-ribono-γ-lactone acetonide. The key steps involved initial ozonolysis, which deletes two carbons, followed by Wittig olefination chemistry to reinstate one carbon. It is against such a background that we now wish to report carbon-atom efficient syntheses of the title compounds from the *cis*-1,2-dihydrocatechols **5**-**7** which are themselves readily obtained in large quantity and high enantiomeric excess by microbial oxidation of the corresponding halobenzene.[10,11]



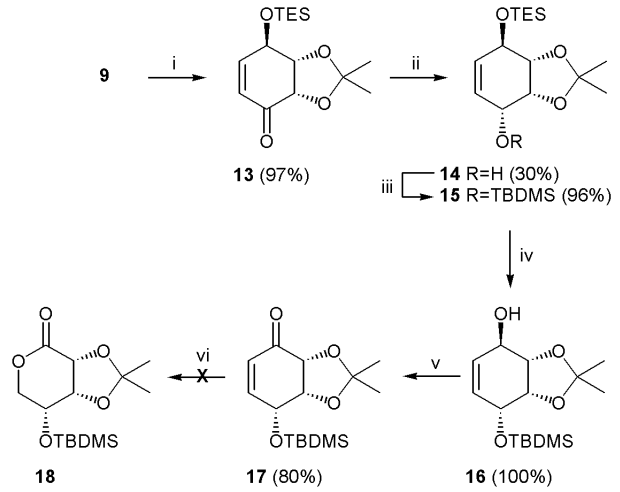


Scheme 1 *Reagents and conditions*: (i) see ref. 12; (ii) see ref. 12; (iii) TBDMSCl (2.95 mole equiv.), Hünig's base (3.8 mole equiv.), DMF, 18 °C, 8 h; (iv) ozone (excess), MeOH, -78 °C, 10 min., then $NaBH_3CN$ (*ca.* 6.0 mole equiv.), HCl (2 M in MeOH), 0 to 18 °C, *ca.* 2.5 h; (v) DIBALH (2.5 mole equiv.), CH_2Cl_2, -78 °C, 2 h then quench with MeOH; (vi) 4:1 v/v TFA/H_2O, 18 °C, 18 h.

A concise synthesis of D-lyxose (**2**) from compound **5** is shown in Scheme 1 and involves initial conversion of the starting material into the corresponding acetonide **8**.[12] This derivative undergoes a β-face selective reaction with singlet-oxygen and the resulting endoperoxide is immediately cleaved with thiourea to give the previously reported[12] γ-hydroxyenone **9** (*ca.* 38% from **5**). In the key step of the reaction sequence, the readily derived *tert*-butyldimethylsilyl (TBDMS)-ether, **10** {80%, m.p. < 50 °C (lit.[12] m.p. = 50-54 °C), $[\alpha]_D$ = -74 (c 5.5)[13]}, of compound **9** was subjected to ozonolytic cleavage followed by a reductive "work-up" using sodium cyanoborohydride at pH 3.[14] In this way the lactone **11** {82%, m.p. = 61-62.5 °C,

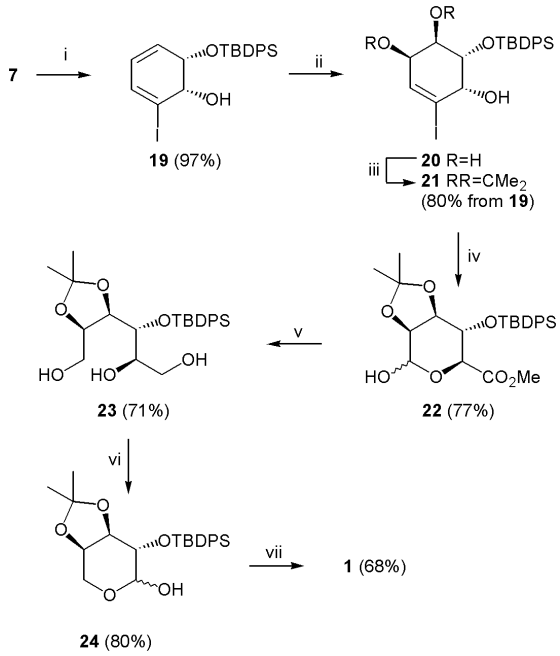
$[\alpha]_D$ = -35 (c 1.6)} was obtained.[15] This last compound was readily converted into the target aldopentose by diisobutylaluminium hydride (DIBALH)-mediated reduction of the lactone moiety to the corresponding lactol **12** {95%, m.p. = 91-91.5 °C, $[\alpha]_D$ = -15 (c 1.0 - rotation determined after 24 h)} which when treated with aqueous trifluoroacetic acid (TFA) afforded D-lyxose (**2**) {82%, m.p. = 115 °C (decomp.), $[\alpha]_D$ = -17 (c 1.0 in H_2O - rotation determined after 25 h)}. This material was identical, in all respects, with an authentic sample obtained from Aldrich™.

Efforts to adapt the above-mentioned chemistry so as to access D-ribose are shown in Scheme 2 and start with the γ-hydroxyenone **9** which was protected as the triethylsilyl (TES)-ether **13** {97%, $[\alpha]_D$ = -38 (c 1.9)} under standard conditions. L-Selectride-mediated reduction of this latter compound provided allylic alcohol **14** {$[\alpha]_D$ = -100 (c 1.8)} as the only isolable product of reaction albeit in 30% yield. Reaction of compound **14** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) in pyridine then gave the TBDMS-ether **15** {96%, $[\alpha]_D$ = -92 (c 1.6)} which upon treatment with aqueous acetic acid in THF resulted in removal of the TES-group to afford alcohol **16** {100%, $[\alpha]_D$ = -97 (c 1.2)}.



Scheme 2 *Reagents and conditions*: (i) TESCl (3 mole equiv.), Hünig's base (4.0 mole equiv.), DMF, 18 °C, 16 h; (ii) L-Selectride (1.1 mole equiv.), THF, -78 °C, 5 min; (iii) TBDMSOTf (3.0 mole equiv.), pyridine (5.0 mole equiv.), CH_2Cl_2, 0-5 °C, 2 h; (iv) 11:5:3 v/v/v AcOH/THF/H_2O, 18 °C, 4 h; (v) TPAP (0.05 mole equiv.), NMO (3 mole equiv.), 4 Å molecular sieves, CH_2Cl_2, 18 °C, 16 h; (vi) ozone (excess), MeOH, -78 °C, 10 min., then $NaBH_3CN$ (*ca*. 6.0 mole equiv.), HCl (2 M in MeOH), 0 to 18 °C, *ca*. 1.5 h. NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate.

Oxidation of the last compound with the Ley-Griffith reagent[16] produced enone **17** {80%, $[\alpha]_D$ = -102 (c 1.0)} but when this material was subjected to the same conditions as used to effect the conversion **10** → **11** the desired D-ribono-δ-lactone derivative **18** could not be detected amongst the complex mixture of reaction products. That analogue of compound **17** in which the TBDMS-group has been replaced by an acetyl moiety also failed to undergo the desired type ozonolytic-cleavage reaction. Consequently, an alternate route from the *cis*-1,2-dihydrocatechols **5**-**7** to D-ribose had to be devised (see Scheme 3).

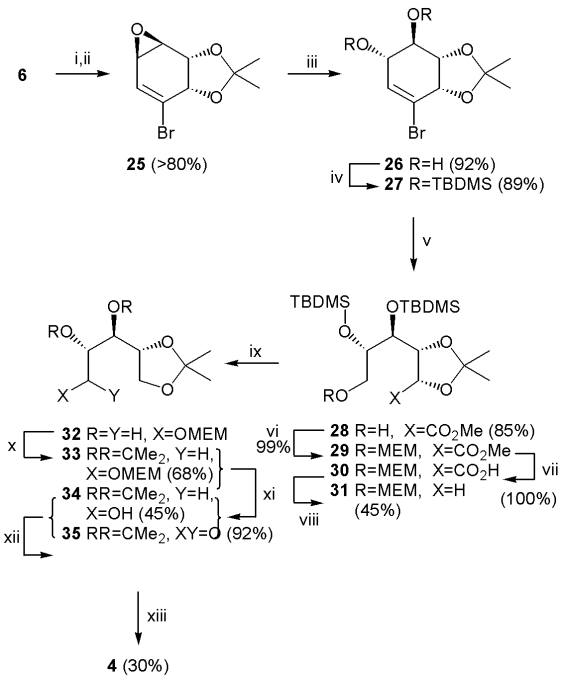


Scheme 3 *Reagents and conditions*: (i) TBDPSCl (1.1 mole equiv.), imidazole (3.0 mole equiv.), CH_2Cl_2, 18 °C, 7 h; (ii) OsO_4 (cat.), NMO (1.3 mole equiv.), 3:1 v/v Me_2CO/H_2O, 4 °C, 30 h; (iii) $Me_2C(OMe)_2$, *p*-TsOH (cat.), 18 °C, 3 h; (iv) ozone (excess), MeOH, -78 °C, 0.5 h then $NaBH_3CN$ (*ca*. 6.0 mole equiv.), HCl (2 M in MeOH), 0 to 18 °C, *ca*. 2.5 h; (v) $LiBH_4$ (5 mole equiv.), MeOH (5 mole equiv.), Et_2O, reflux, 6 h; (vi) $NaIO_4$ (2 mole equiv.), 3:1 v/v MeOH/H_2O, 18 °C, 3 h; (vii) 10% v/v aq. HCl, 18 °C, 18 h.

A reaction sequence for the conversion of monochiral diol **7** into D-arabinose is shown in Scheme 3 and serves to highlight an alternate one-carbon deletion process that allows for the conversion of *cis*-1,2-dihydrocatechols into aldopentoses. Thus, reaction of compound **7** with *tert*-butyldiphenylsilyl (TBDPS)-chloride under carefully controlled conditions resulted in selective protection of the less-hindered hydroxyl group within the substrate and the formation of the rather unstable ether **19** (97%). Diastereofacially-selective *cis*-1,2-dihydroxylation of the latter compound could be effected under standard conditions[17] and the resulting diol **20** was immediately converted, by conventional means, into the corresponding acetonide **21** {*ca*. 80% from **19**, m.p. < 25 °C, $[\alpha]_D$ = +19 (c 1.4)}. Reaction of compound **21** with ozone in methanol followed by a reductive "work-up" using sodium cyanoborohydride at low pH provided the methyl ester **22** {77%, m.p. = 145-147 and 156-158 °C, $[\alpha]_D$ = +41 (c 1.3, determined after 64 h)}. The structure of compound **22** was confirmed by sin-

gle crystal X-ray analysis[18] of its α-anomer which crystallised from mixtures of 1,2-dimethoxyethane and hexane.

Reduction of both the ester and lactol moieties within compound **22** was effected with lithium borohydride and the resulting triol **23** {71%, $[\alpha]_D$ = +28 (c 3.9)} was subjected to oxidative cleavage using sodium metaperiodate thereby producing a protected form, **24** {80%, $[\alpha]_D$ = -24 (c 3.5 - determined after 30 h)}, of target **1**. Treatment of lactol **24** with 10% aqueous HCl then provided D-arabinose itself {68%, m.p. = 158 °C (decomp.), $[\alpha]_D$ = -104 (c 1.0, H_2O - determined after 48 h)} which was identical, in all respects, with an authentic sample obtained from Aldrich™.



Scheme 4 *Reagents and conditions*: (i) ref 20; (ii) ref 20; (iii) 1% v/v HCl in THF, 2:1 v/v THF/H_2O, 18 °C, 16 h; (iv) TBDMSOTf (3.6 mmol), 2,6-lutidine (6.0 mole equiv.), CH_2Cl_2, 18 °C, 18 h; (v) ozone (excess), 1:1 v/v MeOH/CH_2Cl_2 , -78 °C, 0.5 h then $NaBH_4$ (4.0 mole equiv.), 0-18 °C, 3.5 h; (vi) MEM-Cl (5.5 mole equiv.), Hünig's base (3.0 mole equiv.), CH_2Cl_2, 18 °C, 18 h; (vii) KOH (3.0 mole equiv.), THF, MeOH, H_2O, 18 °C, 18 h then 10% v/v aq. HCl; (viii) 2-mercaptopyridine *N*-oxide (1.15 mole equiv.), DCC (1.0 mole equiv.), Et_2O, 18 °C, 2 h then *tert*-dodecanethiol (1.86 mole equiv.), irradiation (400 W high pressure Hg lamp), 18 °C, 2h; (ix) TBAF (4.0 mole equiv.), THF, 18 °C, 18 h; (x) $Me_2C(OMe)_2$, *p*-TsOH (cat.), 18 °C, 3 h; (xi) *n*-BuLi (4.0 mole equiv.), THF, 18 °C, 10 h then $Hg(OAc)_2$ (2.5 mole equiv.), 1:1 v/v THF/H_2O, 18 °C, 5 h; (xii) Dess-Martin periodinane (2.5 mole equiv.), CH_2Cl_2, 18 °C, 1.5 h; (xiii) 6% v/v aq. HCl, 18 °C, 18 h. TBAF = tetra-*n*-butylammonium fluoride.

The acquisition of D-arabinose (**1**) by the method just described also constitutes a formal total synthesis of D-ribose (**3**) from non-carbohydrate sources since treatment of the L-enantiomer of the former compound with molybdenum(VI) oxide bis-2,4-pentanedionate has been shown[19] to provide the L-enantiomer of the latter in *ca.* 28% yield.

Developing a synthesis of D-xylose (**4**) from the *cis*-1,2-dihydrocatechols proved the most demanding aspect of the present work and, ultimately, a radical-decarboxylation process was used to effect the necessary one-carbon deletion step. The initial stages of the synthesis (Scheme 4) involved epoxidation of the acetonide derivative of bromodiol **6** so as to generate the previously reported[20] oxirane **25** (>80% from **6**). Ring-opening of the epoxide moiety within the latter compound could be achieved using water as the nucleophile and HCl as catalyst so as to produce the previously reported[21] *trans*-diol **26** {92%, m.p. = 147 °C, $[\alpha]_D$ = -4 (c 1.0)}. The regioselectivity exhibited in this conversion is consistent with related cleavages of similar epoxides[22] where-in the newly introduced hydroxyl group derives from attack of the nucleophile at the allylic position within substrate **25**. Compound **26** was converted into the corresponding *bis*-TBDMS-ether **27**{89%, m.p. = 101.5-102.5 °C, $[\alpha]_D$ = +43 (c 1.1)} and this latter compound subjected to ozonolysis in methanol then "work-up" with sodium borohydride. In this fashion the hydroxy-ester **28** {85%, $[\alpha]_D$ = -10 (c 10.0)} was obtained and could be converted into the corresponding 2-methoxyethoxymethyl (MEM)-ether **29** {99%, $[\alpha]_D$ = -4 (c 1.9)} under standard conditions. Using the carefully controlled conditions reported by Crich[23] the ester moiety within this latter compound could be converted into the corresponding acid **30** {100%, $[\alpha]_D$ = -9 (c 1.7)} without any complications arising from cleavage of the silyl ether units.

The ester derived from condensation of acid **30** with 2-mercaptopyridine *N*-oxide was then photolysed in the presence of *tert*-dodecanethiol[23] to afford the radical decarboxylation product **31** {45% from **30**, $[\alpha]_D$ = -31 (c 0.7)} which was desilylated under standard conditions and the resulting *vic*-diol **32** immediately reprotected as the corresponding acetonide **33** {68% from **31**, $[\alpha]_D$ = -9 (c 0.2)}. Removal of the MEM-group within this last compound was achieved by sequential treatment with *n*-BuLi then $Hg(OAc)_2$[24] and the resulting xylitol derivative **34** {45%, $[\alpha]_D$ = -12 (c 2.5, MeOH)}[25] oxidised to the aldehyde **35** {92%}[26] using the Dess-Martin periodinane.[27] Finally, deprotection of the last compound using aqueous hydrochloric acid afforded D-xylose (**4**) itself (30%) the tetra-*O*-acetyl-β-D-pyranose derivative {m.p. = 127-128 °C, $[\alpha]_D$ = -23 (c 0.5)} of which proved identical with an authentic sample {m.p. = 126-127 °C, $[\alpha]_D$ = -25 (c 2.0)}[28] derived from commercially available D-xylose.

The work described here-in, especially when considered alongside previous reports from these[29] and other laboratories,[5,11] should serve to emphasise the considerable utility and potential of *cis*-1,2-dihydrocatechols as starting materials for the synthesis of monosaccharides and various derivatives there-of.

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