Synthesis of 3,5-Anhydro-2-deoxy-1,4-glyconolactones by Palladium(II)-Catalyzed, Regioselective Oxy carbonylation of C5- and C6-Enitols. α-Homologation of Aldoses to Produce Intermediates for C-Glycoside/C-Nucleoside Synthesis

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Dedicated to Prof. H. J. Bestmann

The palladium(II)-catalyzed oxy carbonylation, known with alkenols and alkenedinitols, is studied with optically active 4-pentenitols (-triol) 1, 7 and 5-hexenitols (-tetrols) 12, 15, 18. Efficient routes for the substrates are provided, mostly from carbohydrate precursors. In all cases, bicyclic 3,6-anhydro-2-deoxy-1,4-glyconolactones, versatile intermediates of C-glycosidic structure, are isolated with high selectivity and in good yield (53–77%). Several minor products (4–14% of regio-/diastereoisomers) from two competing pathways are observed and identified. The oxy carbonylation of alkenitols thus completes a novel sequence that transforms aldoses into homologous anhydro-glyconolactones, by C1-elongation at the terminal site. In the key step, the 3,4-three arrangement is produced, from each of the four diastereomeric-alkenitols studied (of the 6 cases available in the C5- and C6-series). The stereochemical protocol is summarized, e.g., by the transition D-glucose (aldose) → D-xylene (hexenitol, 15) → l-ido (anhydro-deoxy-heptenolactone 26), as demonstrated.

The homologation of monosaccharides has received much attention since many ‘higher’ carbohydrates, up to C11, are known, and mostly show significant physiological activity.5 Furanosidic or pyranosidic derivatives of such higher carbon sugars, natural or unnatural, are also represented by, or may be viewed as, intermediates for syntheses of C-glycosides.3,4 C-disaccharides,5 C-nucleosides,3,4 or substituted tetrahydrofurans present in many ionophore antibiotics.6 Approaches to elongate the carbon skeleton of carbohydrates or derived material by functionalized C-units inevitably face problems of selectivity, i.e., of chemo-, regio- and/or stereo-differentiation. Of these, (i) to suitably arrange the mandatory pattern of temporarily deactivating, “protecting” groups for the respective substrate, and (ii), to establish the proper configuration at the ‘anomeric’ centre of the C-glycosidic product, have remained a challenge, despite many respective efforts and several promising advances.7-13

We present here a new, general approach to optically active anhydrodiolitols,14-18 a class of compounds that have proven most versatile intermediates for such syntheses.14,15 Our entry into this field features the palladium(II)-catalyzed oxy carbonylation of unprotected enitols as a key step. It is based on findings by Tamara Yoshida and co-workers, with respective reactions of 3-butenols and 3-pentene-1,3-diol,19,20 and by Semmelhack et al. with 4-pentenols,21,22 5-hexenols, and 5-hexene-1,4-diol.23 Each one of these shows its own, peculiar mode of regioselective CO incorporation, with stereoselectivities ranging from high to negligible, see Table 1.24-29

Optically active 5-hexenitols, i.e., 5-hexene-1,2,3,4-tetrols, comprise all of these structural features. In submitting such substrates to the Pd(II)/CO system, the main question therefore is if one of the above pathways would take precedence of the others to a preparatively useful extent. Since the regio- and diastere-differentiation might be governed by the configuration of the ene-polyol substrate, this second aspect was to be addressed by securing and employing different C5- and C6-enitol diastereomers.

Enitols represent a class of carbohydrate derivatives, that is readily available (vide infra) but has hardly found applications in synthesis. Previously, we have provided access to C5 erythro compounds 1 and the like, both from carbohydrate (D-ribonolactone)10-14 and achiral precursors (1,4-pentadien-3-ol, as a unique achiral substrate for asymmetric Sharpless epoxidation).15,30 The studies were started in conjunction with questions related to the stereoselectivity of nitrite oxide cycloadditions30,33 and to the design of superior amino/iminopolyketone syntheses34,35.

The three diasteromer 7, required for the present study, was obtained via the Sharpless product 2 (erythro) likewise. Since 2 and its regio-/diasteromer 3 (threo) are available in either enantiomeric form,30,32,33 any clean substitution at C-2 or C-3 by OH (or an equivalent O-nucleophile) with inversion in 2 or retention in 3, would give access to one or the other enantiomer of the required threo isomer 7. Four protocols to achieve this transform-

| Table 1. Known Types of Pd(II)-Catalyzed Carbonylation of Alkenols |
|------------------------|------------------|------------------|------------------|
| Substrate | Product(s) | Stereochemical Outcome | Ref. |
| 3-butenols | | cis + trans | 19, 20 |
| 4-pentenols | | cis + trans | 21 |
| 5-hexenols | | cis | 22 |
| 5-hexene-1,3-diol | | cis* | 19, 20 |
| 5-hexene-1,4-diol | | cis | 23 |

* Or
ations were studied: (i) Trost's method, Pd(0)-catalyzed, stereoretenti ve carboxylation of vinyl-epoxides, successful with the 1-O-tosylate of 3 in Scharfs group;\textsuperscript{36} (ii) carboxylation catalyzed by cesium carbonate, with inversion at C-2;\textsuperscript{37} (iii) double inversion at C-3 of the internal epoxide 3, first by chloride,\textsuperscript{38} then by hydrolysis of 4, as had been successful for the preparation of 3-amino-4-pentenediols;\textsuperscript{39} (iv) inversion at C-2 via the epoxyurethane 5 derived from 2.\textsuperscript{38,39} Of these, the latter method\textsuperscript{39} proved the most satisfactory and gave the threo-triol 7, after hydrolysis of the intermediate 2,3-carbonate 6, in 55% yield from 2, see Scheme 1. The optical purity of 7 was expected to be ca. 96:4 (e.r.), as judged from capillary GC analysis of 1 reported earlier,\textsuperscript{30,32} and assuming a uniform reaction course. Indeed, the specific rotation found for 7 compares very well with a previous estimate from a 1/7 mixture obtained from glyceraldehyde.\textsuperscript{32}

The C\textsubscript{6} substrates, the hexenitols 12, 15 and 18, were prepared from D-mannitol and monoacetone D-glucose, adopting known routes to the protected olefinic intermediates 11,\textsuperscript{40} 13,\textsuperscript{41} and 16,\textsuperscript{42} see Scheme 2. Hydrolysis for these cases was effected with aqueous acetic acid,\textsuperscript{43} to afford the lyxo-hexenitol 12 and the unsaturated aldoses 14 and 17. Sodium borohydride reduction of the latter went smoothly, although the removal of byproducts (borate) necessitated passage through acidic, then basic ion exchange resins.\textsuperscript{44} The enitols 12,\textsuperscript{40,45} 15\textsuperscript{46} had been obtained previously by less efficient routes (cf.
Experimental Section). The dideoxy-hexoses 14 and 17, respectively, to the best of our knowledge have not been reported in the literature yet; we expect these to be highly interesting, versatile building blocks in other areas likewise.

The oxycarbonylation of these enol substrates was carried out with palladium(II) chloride (catalyst, 0.1 equiv.), copper(II) chloride (oxidant, 3 equiv.) and sodium acetate (buffer, 3 equiv.) in acetic acid under carbon monoxide at normal pressure and room temperature. This system, used in various Pd(II)-catalyzed reactions earlier, had been shown to be advantageous for several intramolecular carbonylations, while dichloromethane/methanol had been the preferred medium for 3-butenol cyclization/dicarbonylation. The enolts used here (see Table 2) on such treatment all underwent slow conversion which could be monitored by colour change of the reaction suspension from green to yellow/ochre; the results are collected in Table 2 and Schemes 3, 4.

The major product in each case was identified by elemental analysis, IR, $^1$H- and $^{13}$C-NMR spectroscopy (Table 1, 3) as the respective 3,6-anhydro-1,4-aldonolactone, isolated in ca. 50–70% yield. With the penentolts 1 and 7, 6 to 11% of a second isomeric product, 20 and 23, respectively, was formed; in the latter case this could be separated from the major product 22 chromatographically.

The mixture of the butyrolactone 19 and bridged valerolactone 20 on reduction with lithium borohydride furnished a single trisubstituted tetrahydrofuran 21 in 66% yield, suggesting that 19/20 were regioisomers. The coupling constants, $J_{2,3} = 5.0$ and $J_{3,4} = 3.9$ Hz, indicate an all-cis configuration in 21, and hence, the L-arabinono configuration of both compounds 19/20. The NMR data obtained for 19 on comparison with those of 22, the butyrolactone formed from the l-threo-pentenitol 7, bear the following evidence: the $^1$H-NMR absorptions of the secondary CHO units at highest field (4.36 and 4.57 ppm, respectively), show a “ddd” and “dd” pattern, respectively; from this and C,H-COSY results the conclusion is, that they originate from the non-acylated CHO-moiety with vicinal CH and CH$_2$ groups, that is they belong to 5-CHOH. With the latter (22), $J_{4,5}$ is not seen (≈ 0 Hz); this is characteristic for a trans arrangement of H nuclei in such systems. The $^{13}$C-NMR chemical shifts obtained from 19/22 likewise indicate, by low-field displacements of the C-4, C-5, C-6 absorptions in 22, the all-cis arrangement of substituents in the tetrahydrofuran part of 19, as viewed against the exo arrangement of OH in 22 with cis,trans-configuration at the tetrahydrofuran ring. The $^1$H- and $^{13}$C-NMR data for 19 and ent-22 that were published during the completion of our study in almost all of the assignments corroborate this interpretation.
### Table 2. Anhydro-2-deoxy-glyconolactones Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenol (configuration)</th>
<th>Product(s) (configuration)</th>
<th>Ratio 1,4-/1,5-Glycono Lac tone</th>
<th>Yield (%)</th>
<th>mp (°C) and/or bp (°C)/mbar</th>
<th>Molecular Formula</th>
<th>IR ν (cm⁻¹)</th>
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<tr>
<td>1</td>
<td>D-1 (D-erythro)</td>
<td>19/20 (L-araabinob)</td>
<td>94:6</td>
<td>68</td>
<td>57-58 140-150/0.01</td>
<td>C₈H₁₄O₄</td>
<td>3660-3040 (br s, OH), 2940 (m), 2860 (m), 1770 (s, CO), 1155 (s), 1070 (s), 1040 (s), 970 (m)</td>
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<tr>
<td>2</td>
<td>L-1 (L-erythro)</td>
<td>ent-19/ent-20 (D-araabinob)</td>
<td>94:6</td>
<td>59</td>
<td>57-58 140-150/0.01</td>
<td>C₈H₁₄O₄</td>
<td>3660-3040 (br s, OH), 2940 (m), 2860 (m), 1770 (s, CO), 1155 (s), 1070 (s), 1040 (s), 970 (m)</td>
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<tr>
<td>3</td>
<td>7 (L-threo)</td>
<td>22/23 (L-xylo/ L-lyxo)</td>
<td>89:11</td>
<td>77</td>
<td>79-81 140-150/0.01</td>
<td>C₈H₁₄O₄</td>
<td>3640-3040 (br s, OH), 2940 (m), 2860 (m), 1760 (s, CO), 1730 (s, CO), 1455 (m), 1180 (s), 1145 (s), 1065 (s), 1035 (s)</td>
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<td>12 (L-lyxo)</td>
<td>24 (D-gluco)</td>
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<td>C₉H₁₈O₅</td>
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<td>5</td>
<td>15 (D-xylol)</td>
<td>26 (L-ido)</td>
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*a Satisfactory microanalyses obtained: C ± 0.32, H ± 0.31.
*b The enantiomerically pure compounds ent-19 and 22 are reported in the reference 16; for ent-19: mp 77-78°C, 22: mp 84-85°C (cf. Experimental Section).
*c IR spectra recorded as a film, except for 25 (CHCl₃).

### Table 3. 'H-NMR Data of Compounds 19–27 Prepared

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<th>Compound</th>
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<th>5-H</th>
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* Recorded at 200.1 (19, 20, ent-19, ent-20) and 250.1 MHz (others) in CD₃OD.
* Values recorded for ent-19 and ent-20 in excellent agreement with those given for the enantiomeric compounds 19, 20.
* Long-range couplings observed in spectra from 19/ent-19 (J₂₀,₂₄ = 0.2 Hz), 20 (J₂₀,₃ = 0.3 Hz), 24 (J₂₄,₃ = 0.3 Hz).
* Not identified due to overlapping signals.
* In DMSO-d₆, the OH absorptions show a doublet each, cf. experimental section.

For numbering schemes and endo/exo-1-H designation cf. stereoformulas 19, 23, 25.
membered lactone with 4-O-acylation to the 6-ring lactone in 20. Similar arguments were applied to assign structure and configuration of 23.

The oxyacylation of the hexenitols 12, 15, and 18 gave the bicyclic ([3.3.0]) butyrolactones 24, 26, and 27 respectively; see Table 2. From the close agreement of the spectroscopic data obtained for 24 with those of the 4-xylo-hexenolactone 22, the configuration of the newly generated stereocentres (C-3, C-4), and hence the d-glucosyl-arrangement in 24 is derived. The products 26 and 27, resulting from the 6-xylo-hexenitols 15 and 18, show 1H- and 13C-NMR data as expected for the change of C-6 configuration from 24 (d-glucosyl) to 26/27 (l-idos). Independent support for these assignments comes from a recent paper on novel bioactive styryl-lactones, notably goniofurfuroe, a 7-phenyl-substituted 3,6-anhydro-2-deoxy-heptonolactone of glycero-idol-configuration (absolute configuration not known),49 the 1H coupling parameters and 13C chemical shifts given there nicely parallel the respective numbers of the l-idos compound 26.

The oxyacylation of the 4-lyxo-hexenitol 12 besides 24 furnished a second isomer, 25, which was obtained pure by chromatographic separation (14% yield). The NMR data, in particular the absorptions of 4-H, 3-H, 5-H, and of C-3 to C-6, showed substantial differences to those recorded for the other two types of anhydro-lactones dealt with so far. From C,H-COSY experiments all proton and carbon resonances were assigned, except for 4-H/5-H and C-4/C-5. The 1H-NMR spectrum taken in DMSO-d6 showed two doublets for the OH signals pointing to the presence of two CHOH fragments; an IR absorption at 1770 cm⁻¹ indicated a 1,4-lactone part. With these pieces of information, 13C-NMR data of substructures – the bicyclic lactones 19/20 and the reduced monocyte 21, pento-pyranoses and their methyl glycosides,49 furanos and anhydroalditols50 – were screened. Surprisingly (vide infra), the unambiguous conclusion was that 25 is 3,7-anhydro-2-deoxy-(D)-gluco-1,4-heptonolactone, with the 4C₁ solution conformation. With branched substrates, erythro/threo-3-hydroxy-methyl-4-pentene-1,4-diols, oxyacyclonony had only resulted in tetrahydrofuran-7/-lactone formation as shown in Table 1; none of the tetrahydrofuran products from the competing cyclization mode had been detectable there.19 On the other hand, such products were the only ones formed from 1,4-diols with an intermittent o-phenylene moiety that does not permit other types of bicyclication (see Table 1).23

The mechanistic course of the fascinating, oxyacylation bicyclization of unsaturated polyols and the likes has not been established in detail yet.19,24,27 This concerns the role and directing power of variously placed OH groups, the reversibility of the several steps prior to CO insertion into the Pd⁻C bond, and the sequence of steps (proven or likely) involved – Pd(II)/C=C coordination, sparking the nucleophile’s attack to form the first ring with a terminal σ-Pd-C species, CO → Pd coordination plus Pd⁻C insertion as the C-elongation step, lactonization to the bicyclic product with extrusion of PdX₃L₃, representing or collapsing to Pd(0), which is reverted to
Pd(II) by the CuCl₂ oxidant, to re-enter the catalytic cycle.⁶⁻²⁴,²⁷ Concerning the aspect "utility for organic synthesis", the above first applications of this reaction to optically active and carbohydrate-derived alkenolits demonstrate that bicyclization to afford anhydroaldonolactones of the [3,3,0]-type is the dominating process, and thus should be taken as a new, viable alternative for homologation of alkenolits, to arrive at C-glycosidic structures in a predictable manner. The principle of the above transformations may be summarized by formulas A and B showing that the configuration at the allylic centre induces the generation of the new stereocentre in a three-selective manner:

![Chemical Structure](image)

Thus, starting from D-glucose (or L-idose), via the D-xylo-xenitol, the anhydro-1,4-heptonolactone 26 of L-ido configuration is produced; starting from D-allose, the L-altro homologue is expected, D-galactose would convert to L-galacto etc.

That there is at least two additional, although minor bicyclization pathways, not due to product equilibration, shows some effect of the substrate configuration that should be elucidated further. It seems highly promising to introduce further (C₆ and higher) alkenolits to this reaction and to provide partially protected substrates for this, in order to arrive at product structures disfavoured from the free polyls, in a regiocontrolled and stereoselective manner.

A conclusion to be drawn from this study is that the Pd(II)-catalyzed carboxylation of complex C,C-unsaturated substrates, loaded with several a priori competing nucleophilic functional groups, may turn out highly selective and be useful in organic synthesis. Unsaturated polyls are at hand in abundance, that is great variety concerning structures, stereoisomers and partially protected congeners, from iso-skeletal precursors as employed here or, for example, Takano's recent extension of the asymmetric Sharpless epoxidation to divinylglycols.⁴¹ Also, access to suitable substrates by (C₆ + C₆), (C₅ + C₅), and (C₄ + C₄)-strategies, e.g. by Wittig methyleneation, vinyl or allyl metal-effected aldehyde C-elongation, is well established²⁻⁴,⁸,⁹ and may be drawn upon anytime’s discretion.

TLC analyses were carried out with Si60 F₂₅₄-coated aluminum sheets (E. Merck) using EtOAc/petroleum ether (bp 30–75°C) mixtures; detection by UV at 254 nm, phosphomolybdc acid (10% in EtOH) or sulfuric acid (40% in H₂O). Silica 32–63 μm (Woelm) was used for flash chromatography, eluents as above. Melting points were determined on a Tottoli apparatus or a heat bar (system Koller) and are uncorrected. Bp’s refer to bath temperatures of Kugelrohr distillations. The optical rotations were measured on a Perkin-Elmer 241 MC polarimeter using the Drude method to calculate [α]Dₐ from the values found for 546 and 579 nm. IR spectra were recorded on a Perkin-Elmer 4120 spectrometer. NMR spectra were obtained from Varian EM 390, Bruker AC 200, 250 and WM 400 spectrometers (H: 90, 200.1, 250.1, 400.1 MHz; C: 50.3, 62.9, 100.6 MHz) with TMS as internal standard (δ = 0.0 ppm); evaluation of 1H-NMR spectra according to 1st order interpretation; multiplicity of 13C-NMR signals from broad band-decoupled or DEPT spectra. endo- and exo-Situated H₃, H₅ are designated H₃, H₅.

Preparation of Enitins D₁₁, l₁₁-7
(2R,3R)-4-Pentenyl-1,2,3-triol (p-br) was prepared from D-ribo-nolactone in 5 steps with 50% overall yield, bp 120–130°C/0.2 mbr, [α]D²⁺ + 27.4° (c = 1.16, MeOH), as reported earlier²⁰,²¹ [Lit.²⁰,²¹ 50%, bp 120–130°C/0.2 mbr, [α]D²⁺ + 27.7° (c = 2.06, MeOH)].

(2R,3S)-4-Pentenyl-1,2,3-triol (l-1) was obtained from 1,4-penta-dien-3-ol by asymmetric Sharpless epoxidation followed by acidic hydrolysis,²⁰,²² ca. 40% overall yield. bp 120–140°C/0.2 mbr, [α]D²⁻ - 22.9° (c = 1.08, MeOH) [Lit.²⁰,²² 37–61%, bp 140–160°C/0.1 mbr, [α]D²⁻ - 25.8° (c = 1.39, MeOH)].

(2R,3S)-Pentenyl-1,2,3-triol (7):
(2R,3S)-3-(Benzylicamino carboxyloxy)-1,2-epoxy-4-pentene (5):
Prepared as described for the enantiomer,²⁵ epoxide ²⁰,²² [1.06 g of a mixture with 6% i-BoOCH/i-BoOH, [α]D²⁺ + 59.1° (c = 1.34, CHCl₃), corresponding to 1.00 g, 10.0 mmol of 2] in CH₂Cl₂ (anhydrous, 60 mL), to which at 0°C benzyl isocyanate (1.60 g, 12.0 mmol) was added; hydrolysis with sat. NaHCO₃ solution (10 mL) after 4 d at r.t. 1% extraction with CH₂Cl₂ (3 × 15 mL), flash chromatographic purification (silica gel, 56 g, column 27 cm × 2 cm; eluent petroleum ether/EtOAc 1:1). Yield of epoxy urethane 5: 2.02 g (87%), yellow, waxy material; [α]D²⁻ - 30.8° (c = 0.60, CHCl₃) [Lit.²⁵ 67%, [α]D²⁻ + 24.6° (c = 0.223, CHCl₃) found for the enantiomer]; 1H- and 13C-NMR data in accord with those recorded for ent-5.³³

C₆H₅N₂O₃ calc. C 66.94  H 6.48  N 6.00
(233.3) found 66.56 6.61 5.98

For cyclization,²⁵ to the epoxy-urethane 5 (1.58 g, 6.80 mmol) in EtO (75 mL) was added dropwise at 0°C Et₂O–BF₃ (2.76 g, 19.5 mmol) within 20 min, causing a colourless precipitate. With continued stirring at 0°C for 2 h, 2N H₂SO₄ (50 mL) is added to form a second phase; the mixture is stirred at r.t. for 17 h. The organic layer is separated, the aqueous layer is extracted with EtO (5 × 20 mL), the organic solvents are combined and dried (Na₂SO₄). After concentration at 30–40°C/20 mbr the remainder is purified by flash chromatography (of above; 28 g of silica, column 22 cm × 1 cm, petroleum ether/EtOAc 6:4); yield of carbonate 6 650 mg (66%), colourless oil; [α]D²⁻ - 70.5° (c = 0.605, CHCl₃) [found for en-6, ent-6] [α]D²⁻ + 69.0° (c = 0.15, CHCl₃). C₆H₄O₃ calc. C 50.00  H 5.60
(144.1) found 49.82 5.73

IR (CHCl₃); υ = 3550, 3380 (br s), 3060 (m), 1795 (vs), 1590 (m), 1360, 1160, 1020 cm⁻¹. ¹H-NMR (CDCl₃); δ = 3.70 (dd, 1H, H-1), 3.80 (br s, 1H, OH), 3.95 (dd, 1H, H-1), 4.40 ("dt", 1H, 2-H), 5.05 (tt, 1H, 3-H), 5.42 (tt, 1H, 4-H), 5.50 (dt, 1H, 5-H), 5.91 (dd, 1H, 4-H). Coupling constants: J₁₂ = 13.1, J₁₂ = 3.5, J₁₂ = 2.9, J₂₃ = 3.5, J₂₃ = 7.0, J₂₅ = J₃₅ = J₅₆ = 0.9, J₄₅ = 10.3, J₅₆ = 17.3 Hz.

Solvents and reagents were purified and dried according to standard procedures. Ion exchange resins (strongly acidic: Lewatit SP 118, H⁵⁺ form; medium basicity: Lewatit MP 64, OH⁻ form; strongly basic: Lewatit M 500 K⁵⁺, OH⁻ form) were obtained from Bayer AG, Leverkusen; CuCl₂ (Aldrich), PdCl₂ (Janssen), monoacetic glucose (Janssen) and D-ribo-nolactone (Fisku) were purchased. 1,4-Pentadien-3-ol was prepared as described²⁰ or purchased from Aldrich. Reactions in acetone at 100°C were carried out in 100 to 250 mL steel autoclaves (Fa. C. Roth, Karlsruhe).
(2S,3S)-Pentene-1,2,3-triol (7):
For acidic hydrolysis\textsuperscript{4-6} the carbonate 6 (230 mg, 1.60 mmol) is heated to reflux for 16 h in MeOH (4.5 mL) with 6N HCl (0.8 mL). After removal of volatiles at ca. 20 mbar H2O (5 mL) is added and the mixture partitioned with CH2Cl2 (5 mL), to separate from lipophilic impurities. The aqueous phase is concentrated in vacuo to leave the triol 7 as a yellow oil, analytically pure; yield 182 mg (96%); \[^{1}H\]NMR (CDCl\textsubscript{3}): \(\delta = 1.30, 1.40 (2 s, 2 x H, 2 CH\textsubscript{2}), 1.41 (6 s, 6 H, 2 CH\textsubscript{2}), 3.75 and 3.95 (AB of ABC, 2H, 1-H), 4.11 (mc, 2H, 3-H), 4.36 ("t", 1H, 4-H), 5.21 and 5.41 (A' of A'B'X, 2H, 6-H and 6'-H), 5.91 (d'X, 1H, 5-H). Coupling constants: \(^{1}J\text{AB} = \ ^{1}J\text{AC} = 7.5, \ ^{1}J\text{BC} = 4.5, ^{1}J\text{AE} = 4.6, ^{1}J\text{DE} = 4.5, ^{1}J\text{OE} = 4.5, ^{1}J\text{OB} = 4.5, ^{1}J\text{OA} = 10.6, ^{1}J\text{OS} = 16.75, \ ^{1}J\text{SA}_{d,e} = 1.25 Hz.

(2R,3S,4R)-5-Hexene-1,2,3,4-tetrol (to-lyxo-5-Hexenial; 12):
An emulsion of the bis(acetone) 11 (1.76 g, 7.71 mmol) in 2N AcOH (15 mL) is heated under reflux for 2 h (TLC control; eluent petroleum ether/EtOAc 8:2). After concentration in vacuo the remainder is dried (desiccator; KOH) to give analytically pure 12 as a colourless powder, yield 11.1 g (97%), mp 147–149°C. From another sample, analytically pure likewise (96% yield): mp 145–146°C; \[^{1}H\]NMR (CDCl\textsubscript{3}): \(\delta = 32.1^\text{a} (c = 1.005, MeOH)\) \[^{13}C\]NMR mp 147–148°C; \[^{13}C\]NMR \(\delta = 33.4^\text{a} (c = 1.0, H_2O)\) IR (KBr): \(\nu = 3280, 1655, 1505, 1070, 1030, 920\) cm\textsuperscript{-1}.

(2R,3S,4R)-5-Hexene-1,2,3,4-tetrol (to-xylo-5-Hexenial; 15):
D-xylo-Hexenial 15 was prepared earlier from d-sorbitol via the bis(ethylene)acetel and the ensuing 5,6-bis(tosylate) in 4 steps and 5% overall yield.\textsuperscript{40} The route presented here affords 16% of 15, after 4 steps from monoacetone glucose.

1,2,3,4-Di-O-isopropylidene-5-methyl-1,2-diols (10):
At rt, MeCl\textsubscript{2} (0.38 mL, 566 mg, 4.90 mmol) in pyridine (1.5 mL) was added dropwise to a pyridine (1.5 mL) solution of 9 (481 mg, 1.80 mmol). After 15 h at 0°C the mixture is poured on ice/water (20 mL) to form a yellow precipitate, which is filtered and crystallized from MeOH; yield 676 mg (90%) of 10, colourless crystals, mp 117.5–118°C; \[^{1}H\]NMR \(\delta = 51.5^\text{a} \ (c = 2.18, CHCl\textsubscript{3})\) \[^{13}C\]NMR \(\delta = 51.5^\text{a} \ (c = 2.18, CHCl\textsubscript{3})\).

(2R,3S,4R)-1,2,3,4-Bis-iso-bis(isopropylidenedioxy)-5-hexene (to-lyxo-5-Hexenial Bis(acetone); 11): Varying the procedure given by Bladen and Owen,\textsuperscript{40} the dimethylenyl 10 (5.00 g, 10.4 mmol) and NaI (15.0 g, 100 mmol) are dissolved in acetone (100 mL) and heated to 100°C for 6.5 h in a 250 mL-autoclave (C. Roth GmbH, Karlsruhe). The mixture is concentrated in vacuo: the dark-red residue is dissolved in CHCl\textsubscript{3} (10 mL) and treated with Na\textsubscript{2}SO\textsubscript{4} solution (10% in H\textsubscript{2}O) until completely decolourised. After separation the aqueous layer is extracted with CHCl\textsubscript{3} (5 x 15 mL), the organic solutes are combined, once more washed with sat. Na\textsubscript{2}SO\textsubscript{4} solution (25 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated (rotary evaporator). The resulting oil is distilled (Kuglerrohr; 70–80°C/1 mbar) to give an orange oil (2.385 g, 100%) which, dissolved in CHCl\textsubscript{3} (5 mL), is again treated with Na\textsubscript{2}SO\textsubscript{4} solution (2 x 10 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Removal of the solvent at 0.01 mbar gives 11 as a colourless, analytically pure oil; yield 2.19 g (92%); \[^{1}H\]NMR \(\delta = 2.53\) (c = 2.98, CHCl\textsubscript{3}), \[^{13}C\]NMR \(\delta = 66.5\) (c = 2.4, CHCl\textsubscript{3}).

(2R,3S,4R)-1,2,3,4,5-Bis-iso-bis(isopropylidenedioxy)-5-hexene (to-xylo-5-Hexenial Bis(acetone); 13): The bis(tosylate) (6.73 g, 12.0 mmol) with NaI (11.2 g, 75.0 mmol) in acetone (100 mL) is heated in an autoclave to 100°C for 14 h, as described.\textsuperscript{40} Yield 8.37 g (35%), colourless crystals, mp 160–161°C \[^{13}C\]NMR \(\delta = 51.5^\text{a} \ (c = 1.1, CHCl\textsubscript{3})\), \[^{13}C\]NMR \(\delta = 51.5^\text{a} \ (c = 1.1, CHCl\textsubscript{3})\). After completion of these studies, we realized and verified that that access to 13 is more conveniently gained by Li\textsubscript{2}H reduction of 16. cf. Lit.\textsuperscript{4} (Vasella).

(2R,3S,4R)-1,2,3,4,5,6-Bis-iso-bis(isopropylidenedioxy)-5-hexene (to-xylo-5-Hexenial Bis(acetone)); 14): The hexenurilacetone acetate 13 (1.867 g, 10.0 mmol), dissolved in acetone HCl (1:1, 25 mL), is heated to 90°C for 18 h (TLC-monitoring). Removal of solvents in vacuo (20 mbar) leaves a yellow oil which is purified by chromatography on silica gel 60 g.; column 1.8 cm x 10 cm, eluent EtOAc). The furanone 14 is obtained as a yellow, but analytically pure oil; yield 1.274 g (87%); \[^{1}H\]NMR \(\delta = 2.9^\text{c} \ (c = 0.850, MeOH).\)

C\textsubscript{12}H\textsubscript{24}O\textsubscript{3} calc. C 49.31 H 6.90 (found 49.52 7.27)

IR (film): \(\nu = 3350, (s, OH), 2922 (m), 2500 (w), 1615 (w), 1420 (m), 1018 (s), 925 (s) cm\textsuperscript{-1}.

1-NMRR (CDCl\textsubscript{3}); \(\delta = 2.31\) and 3.77 and 3.94–3.99 (2 m, 11 eth), 2-H, 3-H, 4.05–4.36 (m, 1 H, 4-H), 4.55–4.62 (m, 1 H, 1-H), 5.16–5.41 (m, 2 H, 6-H), 5.82–6.09 (m, 1 H, 5-H).

1-C-NMRR (CDCl\textsubscript{3}), mixture of 4 isomers (7): \(\delta = 74.06, 74.31, 74.37, 74.46, 75.49, 75.60, 77.97, 78.82, 81.73, 82.23, 84.84 (all d; C-2, C-3, C-4), 97.76, 99.21, 99.47, 104.17 (all d, relative peak intensities
44: 8: 38: 10: C-1), 117.52, 117.60, 118.46, 118.51 (all t, the latter two stem from the major products; C-6), 135.64, 136.06, 139.03 (all d, C-5).

**2.35.34.5**-**5-Hexene-1,2,3,4-tetrol (15):**
The aldofuranone 14 (908 mg, 6.21 mmol) dissolved in H₂O (10 mL), at r.t. is slowly ca. 20 min) added to a solution of NaB₄H₄ (235 mg, 6.21 mmol) in H₂O (10 mL). The mixture is stirred until gas evolution ceases (ca. 90 min), with the pH of the solution changing from 9 to 10. H₂O (50 mL) and conc. H₂SO₄ (several drops) are added to attain pH 6–7. The resulting solution is passed through columns (8 cm x 18 cm) loaded with ion exchange resins (Lewatit SPC 118, H⁺-form, strongly acidic, 12 g; then Lewatit MP 64, H⁺-form, medium basicity, 12 g). The eluate is concentrated in vacuo (20 mbar) and leaves a spectroscopically and analytically pure, colourless oil 15; yield 592 mg (64%); [α]D₂4 + 16.2° (c = 0.550, MeOH).

**IR (film):** ν = 3340 (s, OH), 2920, 2880, 2480 (s), 2068, 1632 (w), 1420, 1012, 970 (s cm⁻¹).

**1H-NMR (CD₃OD):** δ = 3.51 (dd, 1H, 3-), 3.59–3.71 (m, 2H, 1-3), 3.74 (mc, 1H, 2-), 4.24 (″dd″, 1H, 4-), 5.23 (dt, 1H, 1-6H), 5.38 (dt, 1H, 6-2H), 5.98 (dd, 1H, 5-1H). Coupling constants: J₁₂₋₃ = 2.6, J₄₋₅ = 6.1, J₅₋₆ = 6.4, J₆₋₇ = 1.3, J₇₋₈ = 10.4, J₈₋₉ = 17.2, J₉₋₁₀ = 1.45 Hz.

**References:**

1. **Alkylcarboxylic acid; 3-6-Alkyl-1,4-diolactones:**

3,6-Alkano-2-deoxy-D-xylo-2-xylohexan-1,4-diolactone (19, 20): Typical Procedure:
A 50 mL-flask, purged with CO and connected to a balloon filled with CO, is charged with PdCl₂ (25 mg, 0.138 mmol), CuCl₂ (anhydrous; 557 mg, 4.14 mmol), Na₂OAc (anhydrous; 340 mg, 4.14 mmol), (2S,3R)-4-pentene-1,2-diol (1, 16, 138 mg, 1.38 mmol), and AcOH (10 mL). The deep green mixture is stirred at r.t. for 16 h (until coloured yellow to ochre), then filtered through a short tube filled with cellulose. AcOH is removed on a rotavapor (20 mbar), the residue is distilled (Kugelrohr, bath temp. 140–150°C/0.01 mmbar); analytically pure colourless oil (136 mg, 68%), solidifying at 7°C; mp 57–58°C, [α]D²⁰ + 84.1° (c = 1.410, MeOH), containing 19 and 20 in a 94: 6 ratio (± 2); by 13C-NMR; Lit. values for the D-xylo-arabinose compound see ent.19.

**References:**

1. **D-xylo-arabinose-1,4- and 1,5-Hexanotetraol-19 and 20:**
The typical procedure detailed for preparation of 19 is used. 1-Tetroxy-Triol 1 (125 mg, 0.166 mmol, with [α]D²⁰ + 22.9°, see above), PdCl₂ (19 mg, 0.11 mmol), CuCl₂ (427 mg, 3.18 mmol), Na₂OAc (260 mg, 3.18 mmol) in AcOH (10 mL); reaction at r.t. for 17 h. Colourless oil that crystallizes on cooling in the refrigerator, 90 mg (59%), mp 57–58°C, bp 140–150°C/0.01 mmbar, [α]D²⁰ + 84.3° (c = 1.36, MeOH) [Lit.]: mp 77–78°C, [α]D³⁰ + 89° (c = 1.0, CHCl₃). The product consists of a 95: 5 mixture of 1,4-/1,5-lactones ent.19/cm-20; all spectroscopic data in close agreement with those recorded for the compounds 19/20 of the l-series (vide supra).

**References:**

1. **1,4-Alkano-2-deoxy-D-xylo-2-xylo-hexan-1,4-diolactone (2S,3R,4S)-2-Hydroxyethyltetrahydrofuran-3,4-dioli**:

A dry (heat-gum) flask is charged with 19 (92: 8 – mixture of 19/20: 100 mg, 0.594 mmol), THF (10 mL), and LiBH₄ (63 mg, 2.9 mmol). The mixture is stirred for 24 h at r.t. under N₂, then neutralized with conc. H₂SO₄ (2 drops). The solution, diluted with H₂O (100 mL), is passed through a column (1.8 cm x 8 cm) filled with strongly acidic (Lewatit SPC 118, 12 g), then a like one with medium-basic ion exchange resin (Lewatit MP 64, 12 g). The solutes are concentrated (20 mbar) to afford a yellow oil consisting of 21 with no other diastereomeric detectable by 13C-NMR (d: r > 95: 5). Analytically pure 21 (colourless oil) is obtained by filtration of the above oil, dissolved in Diethyl ether through silica (20 g, column 1.8 cm x 10 cm), followed by dried (P₂O₅, 0.01 mbar). Yield 65 mg (66%); [α]D²⁰ + 9.6° (c = 1.295, MeOH).

**References:**

1. **C₆H₄O₄ Na calc. C 48.64 H 8.16 (2H₄) found 48.87 8.46

IR (film): ν = 3340 (br s, OH), 2960, 2880, 1410, 1105, 1005 (all m) cm⁻¹.
3,6-Anhydro-deoxy-β-D-ribofuranose-1,4,6-tri-6-deoxy-1,4,6-tri-8-hexanoyloxy-2,6-dioxo-2,6-dixicyclo[3.3.0]octan-3-one (27): Following the typical procedure, mesyl-tetrol 18 (434 mg, 1.92 mmol), PdCl₂ (34 mg, 0.19 mmol), CuCl₂ (774 mg, 5.75 mmol), NaOAc (472 mg, 5.75 mmol), AcOH (10 mL); reaction under CO for 21 h at r.t., until the green colour has turned orange. The crude product, a yellow oil (666 mg), is chromatographed (silica gel, 20 g, column 1.8 cm x 10 cm); eluent EtOAc); yield of 27 as a yellow oil 327 mg (67%), [α]D25 -28.5° (c = 0.880, MeOH), Rf 0.36 (EtOAc).

This work was supported by the A. v. Humboldt-Stiftung by awarding post-doc fellowship to T. Graça (Bratislava) in 1988 and 1991. We are also grateful for financial support from Fonds der Chemischen Industrie and Bundesgesundheitsamt/AIDS-Forschungsförderung des BMFT, Berlin, and for generous supply of chemicals by Bayer AG, Wuppertal (H. Meyer, H. Bösgen) and Degussa AG, Hanau (K. Dracz). We are further obliged to Marietta Schwarz and also toThomas Baum and Kathi Wurm (Participants of undergraduate research programs 1990 and 1991, respectively) for carrying out several experiments.

Received: 4 September 1991


(8) Many examples may be found in Ref. 2–4. A selection of further work is given in the following references.

(9) C-Glycoside structures from Wittig reactions:

Ohnie, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Chris-

(10) C-Glycosyl structures from vinyl, allyl and fuly metal derivatives, see, for example:


(14) See for example Ref. 3, 4, 8 (Ohru).

Further uses, after optical resolution:

(16) L-lyx- and D-arabino-3,6-anhydro-2-deoxy-hexanotetraoses:

(17) Synthesis of precursors:

(18) Cf. 3,6-anhydro-l-gulono- and -idono-lactones:


For a review see:

(23) For reviews on Pd(II)-mediated chemistry see:

(24) For other transition metal-porovolcarbonyl complexes of carboxylate substrates with Co-, Fe-, Mn-carbonyl complexes see:
Ref. 13 (Mn) and references cited therein.

(25) For an authoritative review on these and other cyclization-functionalizations see:

(26) For related intramolecular amidocarbonylations see:
See also Ref. 24 and 28.

(27) For related intramolecular amidocarbonylations see:
(50) A beautiful collection of carbohydrate $^{13}$C-NMR data is presented by: