Facile Synthesis of Enantiomerically Pure Carbafuranoses: Precursors of Carbocyclic Nucleosides

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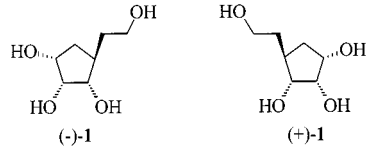
Keywords: Carbocycles / Nucleosides / Carbohydrates / Cyclizations / Mercury

An efficient and highly diastereoselective synthetic approach to enantiomerically pure (–)-(1*R*,2*R*,3*S*,4*R*)- and (+)-(1*S*,2*S*,3*R*,4*S*)-4-hydroxyethylcyclopentane-1,2,3-triols is reported, which involves conversion of D-ribose or D-arabinose to (+)- or (–)-ethyl *Z*-4,5-isopropylidenedioxyhepta-2,6-dienoate, mercuration of the terminal double bond by mercury(II) acetate, followed by reductive radical cyclization and further standard reduction and deprotection manipulations.

Introduction

Chiral polyoxygenated cyclopentanes are substructures of many bioactive compounds, such as glycosidase inhibitors,[1] carbocyclic nucleosides[2] and prostaglandins.[3] They are also referred to as carbafuranoses, and considered as carbohydrate mimics in which the ring oxygen of a furanose has been replaced by a methylene group.[4] 4-Hydroxyethylcyclopentane-1,2,3-triols (or 5-deoxycarbahexofuranoses) and related compounds have attracted considerable attention[5] since they are useful synthetic intermediates in the construction of carbocyclic nucleosides, aminocyclopentitols, carbapentofuranoses, prostaglandin precursors, and other polyoxygenated carbocyclic derivatives. Among the 4-hydroxyethylcyclopentane-1,2,3-triols known, the α-D-ribose mimic (+)-**1** and its β-anomer have been used as intermediates in the synthesis of the carbocyclic nucleosides (−)-aristeromycin and (−)-5′-*homo*-aristeromycin, and the sugar part of carbapolyoxines and carbanikkomycins.[6]

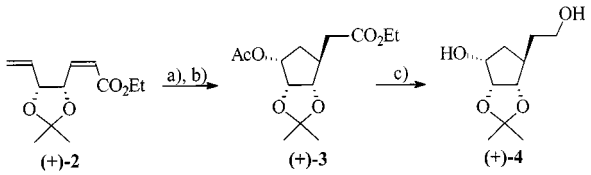


Carbocyclic ring closure of sugar templates is the most popular way to prepare chiral polyhydroxylated carbocycles.[7] The intramolecular radical cyclisation methods to 4-hydroxyethylcyclopentane-1,2,3-triols require conversion of the starting sugar to a 7-bromo- or 7-iodo-2,3-unsaturated ester or lactone and further radical generation at the 7-position by application of the Bu_3SnH or SmI_2 protocols, followed by intramolecular Michael addition.[5,6,8]

We now report a new short, efficient and highly diastereoselective method for preparation of 4-hydroxyethylcyclopentane-1,2,3-triols from carbohydrates, which involves: (i) conversion of the sugar to a *Z*-hepta-2,6-dienoate derivative, (ii) mercuration of the terminal double bond by $Hg(OAc)_2$ followed by reductive radical cyclisation according to standard procedures,[9] and (iii) further standard reduction and deprotection manipulations. Our approach to carbafuranoses is exemplified by reporting here the synthesis of enantiomerically pure (1*R*,2*R*,3*S*,4*R*)- and (1*S*,2*S*,3*R*,4*S*)-4-hydroxyethylcyclopentane-1,2,3-triols, (−)-**1** and (+)-**1**, as outlined in Schemes 1 and 3, respectively.

Results and Discussion

We recently reported the synthesis of the hepta-2,6-dienoate ester (+)-**2** in three steps from D-ribose in good overall yield.[10] The mercuration of the terminal double bond in the *Z*-isomer (+)-**2** was highly regio- and diastereoselective; the product, without isolation, was treated with $NaHB(OMe)_3$ to give, in good total yield, the cyclized product (+)-**3** as a single diastereoisomer, as shown by ^1H and ^{13}C NMR spectra. A lower yield of the final product was obtained when $NaBH_4$ was used instead of $NaHB(OMe)_3$. The structure of the product was unequivocally assigned by its analytical and spectral data, which were identical to those reported in the literature.[8e] Further reduction of (+)-**3** with $LiAlH_4$ afforded the known protected tetrol (+)-**4** (Scheme 1),[5a] which could be converted into (−)-**1** according to literature procedures.[5a]



Scheme 1. a) $Hg(OAc)_2$, AcOH, 20 °C, 12 h; b) $NaBH(OMe)_3$, CH_2Cl_2, 20 °C, 24 h, 53% from **2**; c) $LiAlH_4$, THF reflux, 5 h, 87%

When the *E*-isomer **5** (Scheme 2) was subjected to the same treatment as the *Z*-isomer (+)-**2**, the cyclization reaction was less selective and an inseparable mixture of diastereoisomers (+)-**3** and **6** was formed in a ratio of approximately 1:2.5.

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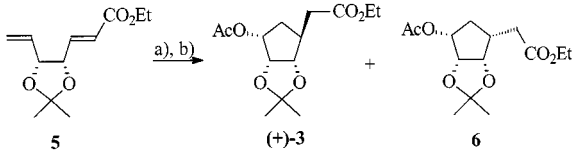
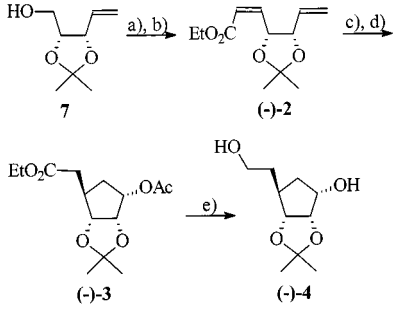


Scheme 2. a) $Hg(OAc)_2$, AcOH, 20 °C, 12 h; b) $NaBH(OMe)_3$, CH_2Cl_2, 20 °C, 24 h, 52%

The influence of the *E*/*Z* geometry on the diastereoselectivity in the carbocyclization of 7-bromo- or 7-iodo-2,3-unsaturated esters by Bu_3SnH or SmI_2 has been thoroughly studied and explanations have been well documented: the *Z*-isomers always give extremely high diastereoselectivity of the *anti*-product relative to the respective *E*-isomers, which usually favor the *syn*-product.[8]

The (1*S*,2*S*,3*R*,4*S*)-4-(2′-hydroxyethyl)-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol, (−)-**4**, which has the correct configuration for the construction of D-carbocyclic nucleosides, was also prepared by a similar manner (Scheme 3). Alcohol **7** was easily obtained from D-arabinose in two steps, with high yield, according to literature procedures.[11] Further Swern oxidation followed by Wittig olefination with $Ph_3P{=}CHCO_2Et$ in EtOH at 0 °C gave the desired (−)-**2**, predominantly in the *Z*-form (*Z*:*E* ca. 7:1). It is known from analogous cases that in a protic solvent (MeOH) at low temperature (0 °C), the *Z*-isomer is predominantly formed with stable phosphorus ylides.[12] Following the procedures discussed in Scheme 1, the synthesis of (−)-**4** was then easily accomplished. It is apparent that the hepta-2,6-dienoate ester (+)-**2** (Scheme 1) could also be prepared from the naturally abundant L-arabinose applying the method used for its enantiomer (−)-**2** (Scheme 3).



Scheme 3. a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −50 °C to 20 °C, 30 min; b) $Ph_3P{=}CHCO_2Et$, EtOH, $PhCO_2H$ (1%), 0 °C−20 °C, 24 h, 75% from **8** (*Z*:*E* ca. 7:1); c) $Hg(OAc)_2$, AcOH, 20 °C, 12 h; d) $NaBH(OMe)_3$, CH_2Cl_2, 20 °C, 24 h, 53%; e) $LiAlH_4$, THF, reflux, 5 h, 87%

Conclusion

A short and efficient method for the synthesis of 4-hydroxyethylcyclopentane-1,2,3-triols from carbohydrates has been developed, as exemplified by the preparation of compounds (+)-**4** and (−)-**4**, which were prepared from D-ribose and D-arabinose, respectively. Conditions for the *Z*-geometry of the intermediate hepta-2,6-dienoate ester — crucial for the subsequent highly diastereoselective radical cyclisation — have been established.

Experimental Section

General: All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. The progress of the reactions was checked by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ glass plates (0.25 mm). The spots were visualized by heat staining with *p*-anisaldehyde in ethanol/sulfuric acid. − Column chromatography was performed with Merck silica gel 60 (0.063−0.200 mm). Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. − The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard.

Ethyl (*Z*,4*R*,5*S*)-4,5-Isopropylidenedioxyhepta-2,6-dienoate [(−)-2]: A solution of dry DMSO (875 mg, 11.2 mmol) in dry CH_2Cl_2 (5 mL) was added to a solution of $(COCl)_2$ (761 mg, 6 mmol) in dry CH_2Cl_2 (10 mL) which had been cooled to −50 °C, under an argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min. before a solution of **7** (637 mg, 4 mmol) in dry CH_2Cl_2 (5 mL) was added carefully over 5 min. while the temperature was kept below −50 °C. The stirring was continued for 20 min., and then dry Et_3N (4.04 g, 40 mmol) was added at the same temperature. After another 15 min. stirring at low temperature, the mixture was allowed to warm to room temperature. CH_2Cl_2 (50 mL) was subsequently added, and the solution was washed with saturated NaCl (2 × 50 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The resulting aldehyde was dissolved in EtOH (40 mL), cooled to 0 °C, and $Ph_3P{=}CHCO_2Et$ (1.675 g, 4.8 mmol) and $PhCO_2H$ (27.5 mg, 0.225 mmol) were added. The solution was stirred at 0 °C for 12 h and then allowed to warm to room temperature. The solvent was subsequently evaporated, and the residue was chromatographed on silica gel with AcOEt/hexane (1:10) as the eluent to give first the *Z*-isomer (−)-**2** as an oil (635 mg, 70%), followed by the *E*-isomer (90 mg, 10%) with spectral data identical to those reported for their enantiomers.[10] For the *Z*-isomer (−)-**2**, $[\alpha]_D = -176.5$ (*c* = 3.4 in $CHCl_3$) {for its enantiomer ref.[10] $[\alpha]_D = +178$ (*c* = 3.9 in $CHCl_3$)}. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 1.41 (s, 3 H), 1.55 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.88 (t, *J* = 6.6 Hz, 1 H), 5.16 (d, *J* = 10.3 Hz, 1 H), 5.28 (d, *J* = 17 Hz, 1 H), 5.61−5.72 (m, 2 H), 5.89 (d, *J* = 11.7 Hz, 1 H), 6.18 (dd, *J* = 11.7 Hz and *J* = 7.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 25.3, 27.7, 60.4, 77.4, 79.7, 109.5, 119.1, 122.6, 133.4, 143.5, 165.9.

(1*R*,2*S*,3*S*,4*S*)-1-*O*-Acetyl-4-ethoxycarbonylmethyl-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol [(+)-3]: $Hg(OAc)_2$ (3.4 g, 10.7 mmol) was added to a solution of (+)-**2**[10] (2.0 g, 8.84 mmol) in glacial acetic acid (20 mL), and the mixture was stirred for 2 days, during which time the reaction progress was monitored by TLC. The solvent was then evaporated, CH_2Cl_2 (10 mL) was added, and the resulting solution was washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and then concentrated in a rotavapor. The residue was dissolved in dry CH_2Cl_2 (20 mL), $NaHB(OMe)_3$ (1.35 g, 10.6 mmol) was added, and the mixture was stirred for 3 days. The solids were filtered, and the solution was washed with H_2O (2 × 20 mL), and dried (Na_2SO_4) After evaporation of the solvent the resulting oil was chromatographed on silica gel with hexane/ethyl

acetate (10:1) as the eluent to give (+)-**3** as an oil (1.34 g, 53%), with ^{1}H and ^{13}C NMR spectral data identical to those reported in the literature.[8e] $[\alpha]_D = +55.4$ ($c = 4.5$ in $CHCl_3$) {ref.[8e] $[\alpha]_D^{19} = +58$ ($c = 1.4$ in $CHCl_3$)}. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (t, $J = 7.3$ Hz, 3 H), 1.31 (s, 3 H), 1.49 (s, 3 H), 1.77 (m, 1 H), 2.11 (s, 3 H), 2.20 (m, 1 H), 2.25 (dd, $J = 15.3$ Hz and $J = 8.4$ Hz, 1 H), 2.34 (dd, $J = 15.3$ Hz and $J = 7.7$ Hz, 1 H), 2.55 (m, 1 H), 4.15 (q, $J = 7.3$ Hz, 2 H), 4.38 (d, $J = 5.7$ Hz, 1 H), 4.69 (t, $J = 5.5$ Hz, 1 H), 4.92 (dd, $J = 9.5$ Hz and $J = 5.5$ Hz, 1 H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 20.8, 24.4, 26.1, 32.5, 36.8, 37.6, 60.6, 73.0, 78.0, 83.9, 111.7, 170.6, 171.7.

(1*S*,2*R*,3*R*,4*R*)-1-*O*-Acetyl-4-(ethoxycarbonylmethyl)-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol [(−)-3]: $Hg(OAc)_2$ (3.4 g, 10.7 mmol) was added to a solution of (−)-**2** (2.0 g, 8.84 mmol) in glacial acetic acid (20 mL), and the mixture was stirred for 2 days, during which time the reaction progress was monitored by TLC. The solvent was then evaporated, CH_2Cl_2 (10 mL) was added, and the resulting solution was washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and then concentrated in a rotavapor. The residue was dissolved in dry CH_2Cl_2 (20 mL), $NaHB(OMe)_3$ (1.35 g, 10.6 mmol) was added, and the mixture was stirred for 3 days. The solids were filtered, and the solution was washed with H_2O (2 × 20 mL), and dried (Na_2SO_4) After evaporation of the solvent the resulting oil was chromatographed on silica gel with hexane/ethyl acetate (10:1) as the eluent to give (−)-**3** as an oil (1.34 g, 53%), with ^{1}H and ^{13}C NMR spectral data identical to those of (+)-**3**. – $[\alpha]_D = -55.0$ ($c = 1.7$ in $CHCl_3$) {for its enantiomer ref.[8e] $[\alpha]_D^{19} = +58$ ($c = 1.4$ in $CHCl_3$)}.

(1*R*,2*S*,3*S*,4*S*)-1-*O*-Acetyl-4-(ethoxycarbonylmethyl)-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol, ((+)-3) and (1*R*,2*S*,3*S*,4*R*)-1-*O*-Acetyl-4-(ethoxycarbonylmethyl)-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol (6): $Hg(OAc)_2$ (1.7 g, 5.35 mmol) was added to a solution of **5**[10] (1.0 g, 4.42 mmol) in glacial acetic acid (10 mL), and the mixture was stirred for 2 days, during which time the reaction progress was monitored by TLC. The solvent was then evaporated, CH_2Cl_2 (10 mL) was added, and the resulting solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and then concentrated in a rotavapor. The residue was dissolved in dry CH_2Cl_2 (10 mL), $NaHB(OMe)_3$ (0.675 g, 5.3 mmol) was added, and the mixture was stirred for 3 days. The solids were filtered, and the solution was washed with H_2O (2 × 20 mL) and dried (Na_2SO_4). After evaporation of the solvent, the resulting oil was chromatographed on silica gel with hexane/ethyl acetate (10:1) as the eluent to give compounds (+)-**3** and **6** as an inseparable mixture (0.657 g, 52%), with ^{1}H and ^{13}C NMR spectral data identical to those reported in the literature.[8e]

(1*R*,2*R*,3*S*,4*R*)-4-(2′-Hydroxyethyl)-2,3-(*O*-isopropylidene)cyclopentane-1,2,3-triol [(+)-4]: $LiAlH_4$ (1.045 g, 27.9 mmol) was added to a solution of (+)-**3** (0.65 g, 2.3 mmol) in dry THF (15 mL), and the mixture was refluxed for 5 h under an argon atmosphere. The excess of $LiAlH_4$ was then destroyed by careful addition of a few drops of H_2O, the mixture was stirred for another 5 min., then filtered, and the solids were washed with MeOH (5 mL). The combined solution was concentrated, and the residue was repeatedly washed with CH_2Cl_2 (5 × 20 mL). The CH_2Cl_2 was then evaporated, and the resulting oil was chromatographed on silica gel with hexane/ethyl acetate (1:2) as the eluent to give **(+)-4** as an oil (0.404 g, 87%), with spectral and analytical data identical to those reported in the literature.[5a] $[\alpha]_D = +14.9$ ($c = 2.9$ in $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (s, 3 H), 1.51 (s, 3 H), 1.55 (m, 2 H), 1.62 (dt, $J = 13.2$ Hz and $J = 6.1$ Hz, 1 H), 1.94 (dt, $J = 13.2$ Hz and $J = 6.5$ Hz, 1 H), 2.05 (br, 1 H, OH), 2.19 (m, 1 H), 2.56 (br, 1 H, OH), 3.69 (t, $J = 6.1$ Hz, 2 H), 4.07 (m, 1 H), 4.36 (dd, $J = 5.9$ Hz and $J = 2.4$ Hz, 1 H), 4.50 (t, $J = 5.9$ Hz, 1 H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.5, 26.1, 35.2, 37.5, 38.8, 61.4, 70.6, 79.5, 85.1, 112.4.

(1*S*,2*S*,3*R*,4*S*)-4-(2′-Hydroxyethyl)-2,3-*O*-isopropylidenecyclopentane-1,2,3-triol [(−)-4]: $LiAlH_4$ (1.045 g, 27.9 mmol) was added to a solution of (−)-**3** (0.65 g, 2.3 mmol) in dry THF (15 mL), and the mixture was refluxed for 5 h under an argon atmosphere. The excess of $LiAlH_4$ was then destroyed by careful addition of a few drops of H_2O, the mixture was stirred for another 5 min., then filtered, and the solids were washed with MeOH (5 mL). The combined solution was concentrated, and the residue was repeatedly washed with CH_2Cl_2 (5 × 20 mL). The CH_2Cl_2 was then evaporated, and the resulting oil was chromatographed on silica gel with hexane/ethyl acetate (1:2) as the eluent to give (+)-**4** as an oil (0.404 g, 87%), with ^{1}H and ^{13}C NMR spectral data identical to those of (+)-**4**. $[\alpha]_D = -15.1$ ($c = 0.7$ in $CHCl_3$).

Acknowledgments

We are grateful to The Hellenic General Secretariat of Research and Technology for financial support of this work.

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Received May 24, 2000
[O00261]