SYNTHESIS OF SUGARS FROM SUBSTITUTED AND UNSUBSTITUTED ARENE DIOLS

Inventor: Tomas Hudlicky, Blacksburg, Va.

Filed: Dec. 6, 1991

Related U.S. Application Data

International Classification: C07G 3/00; C07G 11/00; C07H 15/00; C07H 17/00

United States Classification: 536/41; 127/34; 127/42; 536/18.5; 536/124

Field of Search: 536/4.1, 18.5, 124; 127/34, 42

Abstract
There are disclosed processes for the synthesis of substituted and unsubstituted arene diols useful in the further synthesis of sugars, sugar derivatives, chiral synthons or amino acids.

29 Claims, 3 Drawing Sheets
Figure 3

A. X=Cl
B. X=Br

Protection

M. X=Cl
D. X=Br

Diacyl
Singlet Oxygen
Ozonolysis

1
Reduction
Wittig

2a X=Cl
2b X=Br

Solvolyis

Expected

Mannose

Expected

D-Ribose

Oxidation"my. Singlet Oxygen

Expected

D-Ribose

Expected

L-Gulose

Ozonolysis

Known

D-Ribose

Hydrolysis

L-Ribose

D-Erythrose

Hydrolysis

L-Erythrose

Hydrolysis

E-Hyddrosis {We oDJ oXÿ-

D-Ribose

Ozonolysis

Expected

L-Gulose

Hydrolysis

L-Ribose

D-Erythrose

Hydrolysis

L-Erythrose
SYNTHESIS OF SUGARS FROM SUBSTITUTED AND UNSUBSTITUTED ARENE DIOLS

This application is a continuation-in-part of application Ser. No. 07/480,891 filed Feb. 16, 1990, now abandoned. This application is related to U.S. Ser. No. 07/636,396 filed Dec. 31, 1990, now abandoned.

The present invention relates to the synthesis of sugars and other chiral synths from substituted and unsubstituted arene diols. Particularly, the present invention relates to synthesis of tetrose, pentose and hexose sugars which are useful for synthesis of other sugars and sugar derivatives.

BACKGROUND OF THE INVENTION


Despite the operational simplicity and complete stereospecificity of the reaction producing such diols, little use of this transformation has been made in organic synthesis, except for a few recent reports. [See for example: Hudlicky et al., J. Am. Chem. Soc. 110:4735 (1988) (used the toluene diol to synthesize enones useful for prostaglandin synthesis, aldehydes which are potential synths for perhydroazulene terpenes, and cyclohexene oxide which is the descarboxbenzoxoxy derivative of crotepoxide); Hudlicky et al., J. Org. Chem. 54:4239 (1989) (used the styrene diol to synthesize zeylena, cyclohexene oxide); Ley et al., Tetrahedron Letters 28:225 (1987) and Tetrahedron Letters 29:5305 (1988) (used the benzene diol to synthesize (+)-pinitol and inositol-1,4,5-triphosphate, respectively); and Johnson and Pennin, J. Am. Chem. Soc. 108:4735 (1986) (reported a four step enantioselective synthesis of a prostaglandin intermediate in the shortest route to PGE2a, which was obtained by combination of the microbiobally derived chiral pool reagents with Johnson's procedure for the attachment of prostaglandin side chains)]. However, the full potential of such diols for synthesis of chiral synths has not yet been fully realized.

At present, most commercially produced sugars (such as tetrose, pentose, hexose, polysaccharides, and derivatives thereof) are derived from natural sources or are produced by arduous chemical synthesis from other sugars. L-sugars have been particularly difficult to obtain by presently available synthetic means.

The currently available processes for production of sugars and their derivatives have proven relatively inefficient and expensive. Thus, there is a need for a simple, efficient and cost effective method for synthesizing sugars and derivatives thereof, as well as for making other chiral synths from readily available materials which can be transformed into the appropriate diols.


SUMMARY OF THE INVENTION

Such needs can be obviated by recognizing in accordance with the present invention, the relationship between arene diols and sugars and by taking advantage of the topological inversion of enantiomers through manipulations of the order of chemical events as shown in the simple example of generating synths 17 and 18 from a single enantiomer 1 derived from chlorobenzene diol A as shown in FIG. 1. Either of the two enantiomers 17 or 18 is generated from a single enantiomer 1 derived by oxidative degradation of chlorobenzene via cis-diol 1. By varying the order and the type of chemical operations at each of the localities (a) and (b) in 1, a net enantioemic transposition takes place. Therefore, through the degree of oxidation at (a) and (b), synthon 1 represents a chiral equivalent of meso-tartaric acid, which itself could not have any application in enantioselective synthesis, whereas the chiral equivalent, synthon 4 plays an important role in enantioelective synthesis.

As shown in the Figures, in accordance with the present invention, arene diols are amenable to conversion to various complex carbohydrates by simple oxidative manipulations. The most important feature of such conversions is the enantiofidefergency of the approach. As shown in FIG. 1, the crossover is possible by selection of the order and the type of transformations of the initially formed lactones of type 1. By the one-carbon loss and two-carbon loss oxidative pathways, more complex sugars can be produced as well. The type of sugar or its diastereomeric configuration can be addressed by well established procedures for chain extension or contraction and by manipulations of specific centers in existing carbohydrates. [See for example: (a) Hanessian, S. Total Synthesis of Natural Products: The Chiron Approach. Baldwin, J. E., Ed.; Organic Chemistry Series, Vol. 3; Pergamon: Oxford, 1983. (b) MacGarvey, G. J., Williams, J. M. J. Am. Chem. Soc. 1985, 107, 1435; (c) Hanessian, S. Aldrichimica Acta, 1989, 22, 3 and (d) Garner, P. Studies in Natural Products Chemistry, Atta-ur-Rahman, ed., 1988, 1A, 397 (Elsevier); (e) Crimmins, M. T.; Hollis, W. G., Jr; O'Mahony, R. Studies in Natural Products Chemistry, Atta-ur-Rahman, ed., 1988, 1A, 435 (Elsevier)].
The present invention provides methods for synthesizing sugars from arene diols which may be obtained as products of microbial oxidation reactions. Such methods are relatively simple and more economical than prior methods for such syntheses. A further advantage is provided by such methods in that sugars can be produced from arenes (such as chlorobenzene, polychlorobenzene, styrene, etc.) which are usually considered to be inexpensive, sometimes toxic, waste products. Thus, such waste or by-products can be converted into useful sugars in accordance with the present invention. The methods disclosed herein also allow simpler schemes for synthesis of L-sugars and provide opportunities at each reaction step where isotopically labelled sugars can be produced by using isotopically labelled reagents. It is understood that amino acids could also be synthesized from the resultant sugars in accordance with known methods, and as such, the invention described herein should not be limited by the nature of the end-product made by these novel pathways. These and other advantages of the present invention will be apparent to those skilled in the art from the disclosure herein.

BRIEF DESCRIPTION OF THE DRAWINGS
FIG. 1 is a generalized scheme for synthesis of a tetrose from an arene diol.
FIG. 2 is a generalized scheme for synthesis of sugars from arene diols.
FIG. 3 is a generalized scheme encompassing the completed synthesis of a given example herein.

DETAILED DISCUSSION
The present invention relates to the recognition that arene cis-diols, especially those derived from halobenzenes, reflect the latent oxidation state and stereoergic constitution of carbohydrates, which can therefore be manufactured from such arene cis-diols. Thus the enzymatic dioxygenation can be viewed as providing a chiral substance that resembles a generalized carbohydrate backbone from which several oxygen functionalities have been removed. The methods of the present invention, as further described below, provide methods for the chemical synthesis of sugars and sugar derivatives from these diols. Further described are novel intermediates derived by the processes of the present invention.

Generally, in accordance with the methods of the present invention, 6-, 5- and 4-carbon sugars are synthesized from the appropriate diol by various permutations and combinations of reactions including, but not limited to, epoxidation, hydroxylation, reduction, carbon center inversion, olefination and cyclization reactions. These reactions add and remove carbon atoms from a given carbon moiety, create chiral carbon centers, provide functionalities (such as hydroxyl, keto, aldehyde, alcohol, acid groups, etc.), change the oxidation state of carbon centers, change the stereometric orientation of arenes and change simple carbon cyclic moieties. Such reactions are individually known in the art, but are described herein for the first time in combination, to produce sugars, sugar derivatives and/or useful chiral synthons from arene diols, which should be considered unusual starting materials for sugar synthesis.

The order in which these various reactions are employed depends upon the product intended as the end result of the synthesis. For different sugars, certain steps may be repeated or may be performed in an order different from that for other sugars. However, examination of the chemical constituents of a desired sugar readily reveals the operations necessary for synthesizing such sugar from a given arene diol as is taught in the examples herein. And it is expected that one skilled in the art could make various end products not specifically exemplified herein, using the methods and novel intermediate compounds described herein.

For example, L- and D-erythrose derivatives 17 and 18 were obtained from 1 by modifying the order of chemical events described above. Reduction of 1 with NaBH₄ gave 17 whereas an olefination, reduction and ozonolysis sequence yielded 18. The key to this divergent strategy is the initial backbone of a latent sugar, such as 1 or A (see FIG. 1) and the recognition that the presence of a halide atom allows distinction between pro-D and pro-L spaces of this molecule.

Hexoses are synthesized from a 6-carbon backbone moiety derived from the 6 carbon arene moiety. Pentoses and tetroses are synthesized from 5- and 4-carbon backbone moieties formed by removing carbon from the 6-carbon arene moiety. Depending upon (a) the substitution, if any, of the arene diol used in a given synthesis, and (b) the type and order of reaction steps used in the conversion of the diol to a sugar, the relevant 6-, 5- or 4-carbon backbone moiety is altered during the various reaction steps to change its functionalities as necessary to produce the desired sugar. In some instances, for example the synthesis of D-erythrose disclosed herein, additional carbons may be added to and removed from the relevant backbone moiety during synthesis. However, for the purpose of the appended claims, reaction and/or manipulation of backbone moieties to which additional carbons have been added is still considered a manipulation of the relevant backbone moiety derived from the arene moiety. For example, the conversion of acid 12 to alcohol 16 as shown in FIG. 3 is a reaction involving the 4-carbon backbone moiety originally derived from the diol A upon the conversion of acetamide AA to hydroxylactone 1 by ozonolysis.

In accordance with the present invention, a method for preparation of carbohydrates is disclosed which recognizes that acetamide AA is a latent synthon for tetroses, pentoses, and hexoses through further, properly controlled, oxidation. For example, as shown in FIG. 2, an oxidation with a net loss of two carbons leads to the above tetrose synthons 1. This two step process (going from AA to 1) is an improvement over the systems known in the art such as described by Bergman, R. et al, J. Chem. Soc. Commun., 865 (1990) and Beer, O. et al, Helvetica Chimica ACTA, 65: 2570 (1982). A one-carbon loss from the enone 8 generated from the endoperoxide 21 is expected to lead to a pentose derivative 40 and 41, while reduction of 8 followed by ozonolysis with no carbon loss should give 43, which may be converted via 44 to the rare sugar D-altrose 42. Once compounds such as 17, 40, 41 and/or 42 have been made by methods described in the present application, other diastereomeric sugar derivatives can be reached from such compounds by application of existing manipulations aimed at the inversion of selected centers as delineated by Hanessian in the chiron-based approach to the synthesis of complex molecules from carbohydrates (see for example, (a) Hanessian, S. Total Synthesis of Natural Products: The Chiron Approach. Baldwin, J. E., Ed.; Organic Chemistry Series, Vol. 3; Pergamon: Oxford, 1983. (b) MacGarvey, G. J., Williams, J. M. J. Am. Chem. Soc. 1985, 107, 1435; (c) Hanessian, S. Aldrichimica Acta, 1989, 22, 3; (c) Garner, F. Studies in

Hexoses can be synthesized from arene diols, for example, as shown in FIG. 2. Appropriate permutations and combinations of reactions to produce the desired functionality in the hexose is dictated by the desired end product.

Pentoses can be synthesized from arene diols by first removing one carbon from the diol (e.g., by the addition of singlet oxygen across the arene moiety (with subsequent degradation by ozonolysis)). The 5-carbon product is then converted into the desired sugar, for example, as shown in FIG. 2. Other examples of pentose synthesis are illustrated in FIG. 3. Appropriate permutations and combinations of reactions to produce the desired functionality in the pentose is dictated by the end product desired.

Similarly, tetroses can be synthesized from arene diols by first removing two carbons from the diol (e.g., by ozonolysis) as shown in FIG. 2. The 4-carbon product is then converted into the desired sugar. Tetrose synthesis is exemplified by the synthesis of L and D-erythrose as shown in FIG. 3. Chlorobenzene was oxidized into the corresponding erythronolactones, which are useful as termini for antibacterial and antiviral agents. It is understood that various amino acids could also be synthesized from sugars produced in accordance with the present invention. Methods for synthesis of amino acids from appropriate sugars are well known in the art (for example, those disclosed in Specialist Periodical Reports, Chem. Soc. London, Vol. 1-14).

The synthesis of both enantiomers of erythrose from a single intermediate 1 as exemplified herein underlines the potential benefits of the enantiodivergent methodology described for the first time herein. Both enantiomers of ribonolactone may be obtained from 12 (L) and 21 (D) respectively, the latter compound is expected to be converted to D-ribose.

Potential conversion of 2a and 3a (FIG. 3) to diastereomeric hexoses is expected. These synthons (2a and 3a) contain a more diversified sugar backbone which may be useful in the synthesis of chiral compounds including, but not limited to, sugars, sugar derivatives, amino acids or chiral synthons, are outlined in FIG. 3. The detail of these syntheses and their structure determinations are described as follows.

(25,3S)-2,3-O-Isopropylidene-1-chlorocyclohexa-4,6-diene AA

to a solution of dienediol A (736.5 mg, 4.646 mmol), in 10 mL of 2,2-dimethoxypropane (DMP)-acetone (3:1) was added a catalytic amount of p-toluenesulfonic acid, and the reaction mixture was stirred at room temperature, protected from moisture, until the mixture became a clear solution. The reaction mixture was then concentrated under reduced pressure, washed with brine (3X5 mL). The organic extracts were dried over sodium sulfate, and the solvent was evaporated, yielding 832 mg (95%) of a colorless liquid: Rf: 0.8 (hexane-ethylacetate, 8:2); [a]_D^25 = +45° (c 0.50, CHCl_3); IR (neat) 2988, 2935, 2898, 1652, 1380 cm^-1; 1H NMR (CDCl_3) δ 6.05 (d, J = 5.5 Hz, 1H), 5.85 (m, 2H), 4.77 (dd, J = 3.4 Hz, J = 8.8 Hz, 1H) 4.57 (dd, J = 8.8 Hz, 1H), 1.36 (s, 6H); ¹³C NMR (CDCl_3) δ 133.3, 124.0, 123.2, 121.6, 106.3, 74.7, 72.6, 26.6, 24.9.
2,3-O-Isopropylidene-D-erythronolactone 1

A solution of diene AA, made by the process described above (94 mg, 0.5 mmol) in 7 mL of ethyl acetate was cooled to -78 °C, and a stream of O₂/₃ was passed through until the persistence of a blue color. Nitrogen was bubbled through the solution to remove the excess ozone. Dimethyl sulfide (DMS, 1.4 mL) was added, and the temperature was immediately raised to 0 °C. The reaction was stirred for 12 h and then diluted with 30 mL of ether. The ether solution was washed with water (1X 5 mL) and brine (1X 5 mL). The solution was concentrated, affording 2,3-O-isopropylidene-D-erythronolactone (80%). After purification (chromatography, ethyl acetate/methanol, 7:3), 82% (80.7 mg) of crude product was obtained (34.4%): Rf 0.2 ppm. Spectral data were in agreement with literature values: [α]DPS = +22.8° (c 2.60, CHCl₃). Spectral data were in agreement with literature values: [α]Dp = +44° (c 4.89, CHCl₃). [See: Lager et al., supra]

30

2,3-O-Isopropylidene-L-erythrose 17

Method A

A solution of 78.4 mg (0.5 mmol) of diene AA (made by the process described above) in 7 mL of methanol-methylene chloride (8:2) was cooled to -78 °C, and a stream of O₂/₃ was passed through until the persistence of a blue color. Nitrogen was bubbled through the solution to remove excess ozone. To the stirred reaction mixture at -78 °C under nitrogen atmosphere, was added 36 mg (0.5 mmol) of NaBH₄, stirring was continued for 1 h, the temperature was raised to 0 °C, and the solution was stirred for an additional hour. After that, 10 drops of a saturated aqueous solution of NH₄Cl was added, and the solvent was removed under reduced pressure, without heating. The semisolid residue was taken up in ethyl acetate (5 mL) and filtered; this operation was repeated twice. The combined organic extracts were evaporated to produce 74 mg of a colorless viscous liquid. Separation by preparative TLC (silica gel; hexanes-ethyl acetate, 6:4) produced the following.

2,3-O-Isopropylidene-4-methyl-L-erythronolactone

(116 mg, 12%): [α]D₂⁵ = -66.35° (c 4.75, MeOH); IR (neat) 2985, 2920, 1710 cm⁻¹; 1H NMR (CDCl₃) δ 5.81 (s, 1H), 4.91 (d, 1H, J = 5.4 Hz), 1.47 (s, 3H), 1.40 (s, 3H); 13C NMR (CDCl₃) δ 174, 114, 99, 95, 80, 74, 27, 26 ppm. Spectral data were in agreement with literature values: [α]Dₚ = +22.8° (c 2.60, CHCl₃). Spectral data were in agreement with literature values: [α]D₂⁵ = +24° (c 1.56, CHCl₃). [See: Lager, W.; Hafele, B. Synthesis 1987, 803.]

2,3-O-Isopropylidene-4-pentenoic Acid 12

To a solution of triphenylmethylphosphonium bromide (1.07 g, 3.0 mmol) in THF was added 3.1 mmol of LAH at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into H₂O (30 mL). The aqueous layer was washed with ether (3x 15 mL) and a solution of 1M H₂SO₄. The organic fraction was concentrated. Purification by Kugelrohr distillation (90°-100° C., 0.005 mm) afforded 103 mg (60%) of the vinyl acid 12 as a colorless oil: [α]D₂⁵ = +22.8° (c 2.60, CHCl₃). Spectral data were in agreement with literature values: [α]D₂⁵ = +44° (c 4.89, CHCl₃). [See: Lager et al., supra.]

2,3-O-Isopropylidene-D-erythrose 18

Pentenol 16 (158 mg, 1.00 mmol) was dissolved in CH₂Cl₂ (10 mL) and ozone was bubbled through the solution at -78 °C until persistence of a blue color. Excess ozone was removed by a stream of N₂. Dimethyl sulfide (0.2 mL) was added, and the solution was stirred for 4 h at room temperature. The reaction mixture was washed with H₂O (5X 5 mL), dried (Na₂SO₄), and concentrated. Purification by flash chromatography (silica gel; EtOAc-hexane, 6:4) afforded 88 mg (0.55 mmol, 55%) of lactol 18: [α]D₂⁵ = -71° (c 3.02, CHCl₃); Rf = 0.50. Spectral data were in agreement with literature values: [α]D₂⁵ = -77° (c 2.09, CHCl₃). [See: Hudlicky, T.; Secoane, G.; Lovelace, T. C. J. Org. Chem. 1988, 53, 2094.] Additionally, this material proved iden-
Olefinic acid 12 (12 mg), O\textsubscript{3}S\textsubscript{2}O (2 drops) acetone (0.5 mL), and H\textsubscript{2}O (100 mL) were mixed and stirred at rt overnight. The mixture was purified by a short silica column to give 4 mg of 19, identical to material obtained by conversion of commercial L-ribonolactone to its acetinide ([α]D = +52°) and NMR.

A solution of diene AA [Gibson et al., supra] (1.915 g, 10.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (75 mL) at 0°C was added mCPBA (1.78 g, 8.2 mmol) portionwise. The solution was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was washed with 15% aq sodium sulfite (2×50 mL), saturated aq sodium bicarbonate (2×50 mL), and water (50 mL), then dried (MgSO\textsubscript{4}), filtered, and concentrated. Unreacted starting material was removed under vacuum leaving 1.50 g (7.3 mmol, 89%) of pure epoxide 20 as a colorless solid: mp=59°—60° C.; [α]D = +0.9° (c 0.4, CHCl\textsubscript{3}); FTIR (KBr) 3444, 1754, 1632 cm\textsuperscript{-1}; 1H NMR (CDCl\textsubscript{3}) δ 6.24 (1H, d, J=2.5), 4.66 (1H, d, J=2.5), 4.34 (m, 2H), 4.18 (br s, 1H), 1.48 (s, 3H), 1.44 (s, 3H); 13C NMR (CDCl\textsubscript{3}) δ 195.1, 148.3, 127.9, 110.1, 79.0, 74.0, 65.9, 27.1, 25.6; mass spectrum (El, 70 eV) m/e (rel intensity) 248 (M+, 0.48), 246 (0.48), 233 (0.67), 231 (0.67), 229 (0.67), 227 (0.71), 161 (0.74), 159 (0.74), 109 (1.00), 81 (0.74); Anal. calcd for C\textsubscript{9}H\textsubscript{11}BrO: C, 43.75; H, 4.49. Found: C, 43.71; H, 4.50.

To a solution of diene AA [Gibson et al., supra] (1.915 g, 10.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (75 mL) at 0°C was added mCPBA (1.78 g, 8.2 mmol) portionwise. The solution was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was washed with 15% aq sodium sulfite (2×50 mL), saturated aq sodium bicarbonate (2×50 mL), and water (50 mL), then dried (MgSO\textsubscript{4}), filtered, and concentrated. Unreacted starting material was removed under vacuum leaving 1.50 g (7.3 mmol, 89%) of pure epoxide 20 as a colorless solid: mp=59°—60° C.; [α]D = +0.9° (c 0.4, CHCl\textsubscript{3}); FTIR (KBr) 3444, 1754, 1632 cm\textsuperscript{-1}; 1H NMR (CDCl\textsubscript{3}) δ 6.24 (1H, d, J=2.5), 4.66 (1H, d, J=2.5), 4.34 (m, 2H), 4.18 (br s, 1H), 1.48 (s, 3H), 1.44 (s, 3H); 13C NMR (CDCl\textsubscript{3}) δ 195.1, 148.3, 127.9, 110.1, 79.0, 74.0, 65.9, 27.1, 25.6; mass spectrum (El, 70 eV) m/e (rel intensity) 248 (M+, 0.48), 246 (0.48), 233 (0.67), 231 (0.67), 229 (0.67), 227 (0.71), 161 (0.74), 159 (0.74), 109 (1.00), 81 (0.74); Anal. calcd for C\textsubscript{9}H\textsubscript{11}BrO: C, 43.75; H, 4.49. Found: C, 43.71; H, 4.50.

To an ice-cooled solution of (1R,4S,5S,6R)-3-Chloro-4,5-di-O-isopropylidene-7-oxa-bicyclo[4.1.0]hept-2-ene 2a in DMSO (5 mL) was added an aqueous solution of 10% KOH (5 mL). The mixture was refluxed for 6 h. The aqueous solution was extracted with EtO\textsubscript{Ac} (6×5 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated to dryness. The diol was purified by FCC (10% H\textsubscript{2}O silica gel, 7:5:2:5, EtO\textsubscript{Ac}/Hexane) and 316 mg (65%, 1.19 mmol) of diol was obtained. The diol was recrystallized from CH\textsubscript{2}Cl\textsubscript{2}/Hexane. [α]D = 0.38 (4.1, EA-H); mp=147.0° C; [α]D = 10.7° (c 0.35, MeOH); IR (KBr) 3506, 3395, 2984, 1647, 1083, 1067 cm\textsuperscript{-1}; 1H-NMR (CDCl\textsubscript{3}) δ 6.24 (1H, d, J = 2.5), 4.66 (1H, d,
J = 6.1, 4.18 (1H, dd, J = 7.9, 6.3), 4.06 (1H, m), 3.74 (1H, t, J = 7.6), 77.6 (CH), 77.0 (CH), 73.1 (CH), 70.9 (CH), 28.0 (CH3), 26.0 (CH3); MS (m/z, relative intensity, Cl) 265 (M+), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13O4Br: C, 40.78; H, 4.94. Found: C, 40.51; H, 4.83.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13CI-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.

6), 249 (14), 189 (100), 170 (50), 161 (20), 111 (70); Anal. Calcd for C9H13Cl-75.0, 76.2, 110.4, 126.9, 132.8; mass spectrum (Cl, 70 eV) m/e (rel intensity) 266 (M+, 0.05), 264 (0.05), 251 (0.90), 249 (0.09), 110 (0.44), 101 (1.00); HRMS calcd for C9H13BrO4: C, 40.76; H, 4.90. Found: C, 40.70; H, 4.90.
a. treating a hydroxylactone \( L \) with triphenylmethylphosphonium bromide in the presence of THF, purifying such mixture to yield \((2S,3S)-2,3\text{-O-isopropylidene-4-pentenoic acid}\) 12;

b. treating said pentenoic acid 12 with LAH in the presence of ether to yield a pentenol, \((2R,3S)-2,3\text{-O-isopropylidene-4-pentenol}\) 16;

c. subjecting said pentenol 16 to ozonolysis in the presence of \(\text{CH}_2\text{Cl}_2\) and adding dimethyl sulfide to yield a lactol, \(\text{2,3-O-isopropylidene-D-erythrose}\) 18

provided that steps (a), (b) and (c) above can be carried out sequentially without isolation of the product of each step.

10. A method for producing \((1R,4S,5R,6S)-1\text{-chloro}-7,8\text{-dioxa-5,6-di-O-isopropylidenebicyclo}[2.2.2]\text{oct-2-ene}\) 21, said method comprising reacting tetr phenylporphine in chloroform with an acetonide, AA, \(\text{2,3-O-isopropylidene-L-erythrose}\) in the presence of oxygen and removing the solvent to afford the endoperoxide 21.

11. A method for producing \((4R,5S,6R)-4\text{-hydroxy}-5,6\text{-di-O-isopropylidene cyclohex-2-en-1-one}\) 8 which comprises treating the endoperoxide 21 produced by the method of claim 10 with thiourea in the presence of MeOH.

12. A method for producing an epoxide useful as an intermediate, said epoxide having the formula:

\[
\begin{align*}
\text{(wherein } X = \text{halogen)}
\end{align*}
\]

(2)

13. A method for producing \((1R,4S,5R,6S)-1\text{-chloro}-7,8\text{-dioxa-5,6-di-O-isopropylidenebicyclo}[2.2.2]\text{hept-2-ene}\) 2a.

14. A method of claim 12 wherein \(X = \text{Cl}\) and the resulting epoxide is \((1R,4S,5S,6R)-3\text{-chloro-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}\) 2a.

15. A method of claim 12 wherein \(X = \text{Br}\) and the resulting epoxide is \((1R,4S,5S,6R)-3\text{-bromo-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}\) 2b.

16. A method for producing \((1R,2R,3S,4S)-5\text{-chloro-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}\) 3a.

17. A method of claim 16 wherein \(X = \text{Br}\) and the resulting diol is \((1R,2R,3S,4S)-5\text{-bromo-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}\) 3b.

18. A method for producing a diol of the formula:

\[
\begin{align*}
\text{(wherein } X = \text{halogen)}
\end{align*}
\]

which comprises adding to the epoxide product produced by the method of claim 12 KOH in the presence of DMSO.

19. A method for producing \((1R,2R,3S,4S)-5\text{-bromo-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}\) which comprises adding to the \((1R,4S,5S,6R)-3\text{-bromo-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}\) 2b produced by the method of claim 14 KOH in the presence of DMSO.

20. A method for making \(L\)-Ribonolactone 19, useful as an intermediate, said process comprising subjecting an olefinic acid of the formula:

\[
\begin{align*}
\text{(wherein } X = \text{halogen)}
\end{align*}
\]

(2)

to dioxgenation in the presence of acetone and water to yield \(L\)-ribonolactone after deprotection of the acetonide.

21. An intermediate compound useful in the synthesis of chiral synthons, said intermediate compound being selected from the group consisting of: \((1R,4S,5R,6S)-1\text{-chboro-7,8-dioxao-5,6-di-O-isopropylidene bicyclo}[2.2.2]\text{oct-2-ene}; \(1R,4S,5S,6S)-1\text{-Bromo-7,8-dioxao-5,6-di-O-isopropylidene bicyclo}[2.2.2]\text{oct-2-ene}; \(4R,5S,6R)-4\text{-hydroxy-5,6-di-O-isopropylidene cyclohex-2-en-1-one}; \(1R,4S,5S,6R)-3\text{-Choro-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}; \(1R,4S,5S,6R)-3\text{-Choro-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}; \(1R,4S,5S,6R)-3\text{-Bromo-4,5-di-O-isopropylidene-7-oxa-bicyclo}[4.1.0]\text{hept-2-ene}; \(1R,2R,3S,4S)-5\text{-Chloro-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}; \(1R,2R,3S,4S)-5\text{-Bromo-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}; \(1S,2R,3S,4S)-5\text{-Bromo-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}; \(1S,2R,3S,4S)-5\text{-Chloro-1,2-dihydroxy-3,4-di-O-isopropylidene cyclohex-5-ene}; \)
(2S,3S)-2,3-O-Isopropylidene-1-chlorocyclohexa-4,6-diene; and 2,3-O-Isopropylidene-D-erythruronolactone.

22. A method for producing L-erythrose, said method comprising:
   a. subjecting (+)-cis-2,3-dihydroxy-1-chloro-cyclohexa-4,6-diene to ozonolysis;
   b. reducing the product of said ozonolysis with sodium borohydride to form 2,3-O-isopropylidene-L-erythrose; and
   c. deprotecting said 2,3-O-isopropylidene-L-erythrose to form L-erythrose.

23. A method for producing L-erythrose, said method comprising:
   a. treating (+)-cis-2,3-dihydroxy-1-chloro-cyclohexa-4,6-diene with p-toluenesulfonic acid in the presence of 2,2-dimethoxypropane to form (2R,3S)-2,3-O-isopropylidene-L-chloro-cyclohexa-4,6-diene;
   b. subjecting said (2R,3S)-2,3-isopropylidene-L-chloro-cyclohexa-4,6-diene to ozonolysis followed by cyclization of the product of said ozonolysis to form 2,3-O-isopropylidene-D-erythruronolactone;
   c. reducing said 2,3-O-isopropylidene-L-erythruronolactone in the presence of sodium borohydride to produce sodium (S,S)-2,3-dihydroxy-2,3-O-isopropylidene-4-hydroxy-butyrate;
   d. cyclizing said sodium (S,S)-2,3-dihydroxy-2,3-O-isopropylidene-4-hydroxy-butyrate in the presence of iodomethane to form 2,3-O-isopropylidene-D-erythronol-1,4-lactone;
   e. subjecting said 2,3-O-isopropylidene-D-erythronolactone to olefination to form (2R,3S)-2,3-0-isopropylidene-4-pentenoic acid;
   f. reducing said (2R,3S)-2,3-O-isopropylidene-4-pentenoic acid in the presence of LAH to form (2R,3S)-2,3-O-isopropylidene-4-penten-1,2,3-triol; and
   g. deprotecting said (2R,3S)-2,3-O-isopropylidene-4-penten-1,2,3-triol to to form D-erythrose.

24. A method of producing D-erythrose, said method comprising:
   a. treating (+)-cis-2,3-dihydroxy-1-chloro-cyclohexa-4,6-diene with p-toluenesulfonic acid in the presence of 2,2-dimethoxypropane to form (2R,3S)-2,3-O-isopropylidene-L-chloro-cyclohexa-4,6-diene;
   b. subjecting said (2R,3S)-2,3-isopropylidene-L-chloro-cyclohexa-4,6-diene to ozonolysis followed by cyclization of the product of said ozonolysis to form 2,3-O-isopropylidene-D-erythruronolactone;
   c. subjecting said 2,3-O-isopropylidene-L-erythruronolactone to olefination to form (2S,3R)-2,3-O-isopropylidene-4-pentenoic acid;
   d. reducing said (2S,3R)-2,3-O-isopropylidene-4-pentenoic acid in the presence of LAH to form (2S,3R)-2,3-O-isopropylidene-4-penten-1,2,3-triol; and
   e. deprotecting said (2S,3R)-2,3-O-isopropylidene-D-erythrose to form L-erythrose.

25. A method of producing L-ribonic gamma lactone, said method comprising:
   a. treating (+)-cis-2,3-dihydroxy-1-chloro-cyclohexa-4,6-diene with p-toluenesulfonic acid in the presence of 2,2-dimethoxypropane to form (2R,3S)-2,3-O-isopropylidene-L-chloro-cyclohexa-4,6-diene;
   b. subjecting said (2R,3S)-2,3-isopropylidene-L-chloro-cyclohexa-4,6-diene to ozonolysis followed by cyclization of the product of said ozonolysis to form 2,3-O-isopropylidene-D-erythruronolactone;
   c. subjecting said 2,3-O-isopropylidene-D-erythruronolactone to olefination to form (2S,3R)-2,3-O-isopropylidene-4-pentenoic acid;
   d. reducing said (2S,3R)-2,3-O-isopropylidene-4-pentenoic acid in the presence of LAH to form (2S,3R)-2,3-O-isopropylidene-4-penten-1,2,3-triol; and
   e. deprotecting said (2S,3R)-2,3-O-isopropylidene-D-erythrose to form L-erythrose.

26. A method for making (2S,3S)-2,3-O-Isopropylidene-1-chlorocyclohexa-4,6-diene useful as an intermediate, said method comprising: reacting a dienediol A with a mixture of 2,2-dimethoxypropane-acetone, in the presence of p-toluenesulfonic acid to yield (2S,3S)-2,3-O-Isopropylidene-1-chlorocyclohexa-4,6-diene.

27. A method for making 2,3-O-Isopropylidene-D-erythruronolactone, useful as an intermediate, said method comprising reacting (2S,3S)-2,3-O-Isopropylidene-1-chlorocyclohexa-4,6-diene, with ethyl acetate and ozone to yield 2,3-O-Isopropylidene-D-erythruronolactone.

28. A method for making (2S,3S)-2,3-O-Isopropylidene-4-pentenoic acid useful as an intermediate, said method comprising:
   a. reacting triphenylmethyl phosphorium bromide in THF with n-BuLi; or
   b. adding 2,3-O-Isopropylidene-D-erythruronolactone in THF with stirring, to yield (2S,3S)-2,3-O-Isopropylidene-4-pentenoic acid.

29. A method for producing (2R,3S)-2,3-O-Isopropylidene-4-pentenol which comprises reacting the (2S,3S)-2,3-O-Isopropylidene-4-pentenoic acid produced by the method of claim 28 in ether, with LAH with stirring and quenching such reaction mixture with water and aqueous NaOH.