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Syntheses of L-threose and D-erythrose analogues modified at position 2

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Abstract

2-O-Methyl-D-erythrose, 2-O-methyl-L-threose, 2-deoxy-D- and L-erythrose, and the corresponding acetonides have been prepared from the commercially available D-isoascorbic and L-ascorbic acids. The proportion of cyclic (α and β furanoses) and acyclic (aldehyde and hydrate) forms was determined in aqueous (D_2O) solution by ^{1}H and ^{13}C NMR spectroscopy.

1. Introduction

Monosaccharides are the chemical units from which all members of the major family of natural products, the carbohydrates, are built. Among monosaccharides, tetroses constitute probably the most poorly characterized group. All of the oldest synthetic procedures involve degradation of an appropriate sugar[1a] or sugar derivative.[1b,c] Among the modern methods[2a] from a non-carbohydrate source, we can note the preparation of L- and D-erythrose acetonides using: (1) microbial metabolites as homochiral starting materials;[2b] (2) D-glyceraldehyde acetonide and an iterative process with the highly stereoselective thiazole addition;[3a,b] (3) the Sharpless asymmetric epoxidation[3c] of allylic alcohols, a now common method used in the construction of sugars.

We focused on the syntheses of substituted butanals, potential substrates of two enzymes, transketolase and fructose-1,6-bisphosphate aldolase (FB-aldolase). These enzymes are interesting and complementary tools for the enzymatic syntheses of monosaccharide analogues by C–C bond forming reactions.[4] Our aim was to synthesize L-threose and D-erythrose analogues, because these compounds are able to lead to close analogues of D-fructose and L-sorbose by transketolase catalysis or to new heptuloses of the D or L series using FB-aldolase. The results concerning this enzymatic study have already been published[5] and, in this paper, we will describe the syntheses of 2-deoxy-D- and L-erythrose **2a** and **2b**, 2-O-methyl-D-erythrose **1a** and 2-O-methyl-L-threose **1b** derivatives and the corresponding acetonides. Compounds

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1a and **1b** have not been described before; **2a** and **2b** have been synthesized before from 3-deoxy-D-erythropentose[6] and from L-malic acid[7] respectively.

We present here the synthesis of **1a** and **1b** starting with inexpensive D-isoascorbic and L-ascorbic acids. These two acids have been used before, especially by Abushanab[8] and Depezay[9] to obtain two butanetriol enantiomers. For the deoxy compound **2a** and **2b**, we first tried the method from L-malic acid[7] but the material obtained in this manner is contaminated by (2S)-2,4-dihydroxybutanal and is difficult to purify. We then developed another method starting with the chiral (S)-2,2-dimethyl-1,3-dioxolane-4-methanol ((S)-solketal) for the obtention of the D isomer **2a**. Finally, as the synthesis of **1a** and **1b** from L-ascorbic and D-isoascorbic acids offers a possible access to both enantiomers of **2**, we decided to explore this path also. In the last part of this study, the proportion of cyclic (α and β furanoses) and acyclic (aldehyde and hydrate) forms of **1a**, **1b**, **2a** and **2b** were determined in aqueous (D_2O) solution by ^1H and ^{13}C NMR spectroscopy.

2. Results and discussion

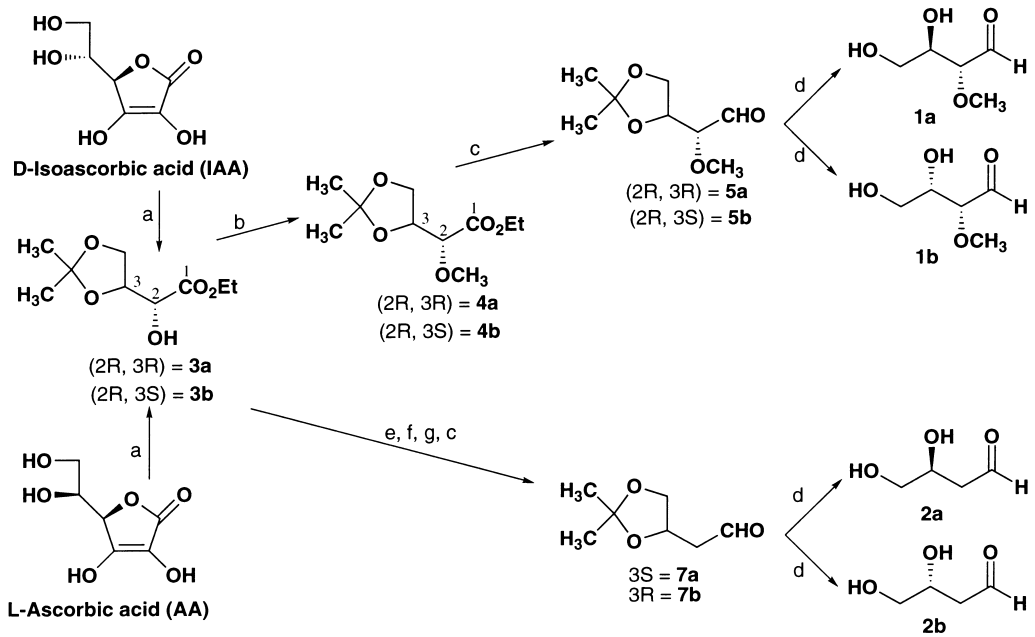
The commercially available D-isoascorbic and L-ascorbic acids were converted, in two steps according to the strategy of Abushanab et al.,[8] into two intermediary synthons containing two stereogenic centers, ethyl (2R,3R)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate **3a** and ethyl (2R,3S)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate **3b** in excellent yields (Scheme 1). In the first step, the starting acid was converted into the acetonide. Cleavage of the double bond with aqueous hydrogen peroxide followed by esterification with ethyl iodide gave the two intermediary esters **3a** and **3b**. Compound **3a** will lead to (S)-3,4-dihydroxybutanal **2a** and (2R,3R)-2-O-methyl-3,4-dihydroxybutanal **1a** (2-deoxy-D-erythrose and 2-O-methyl-D-erythrose) and, by the same reactions, **3b** will lead to (R)-3,4-dihydroxybutanal **2b** and (2R,3S)-2-O-methyl-3,4-dihydroxybutanal **1b** (2-deoxy-L-erythrose and 2-O-methyl-L-threose) and the corresponding acetonides.

*2.1. Syntheses of 2-O-methyl-D-erythrose **1a** and 2-O-methyl-L-threose **1b** and the corresponding acetonides **5a** and **5b***

Among the numerous procedures of alkylation of hydroxyl groups described in the literature, it appears that the methylation using methyl iodide and silver oxide[10] is the most efficient for substrates possessing a lactone or an ester group. In the process described here, the hydroxyester and the alkyl iodide were simply dissolved in dry acetonitrile. Powdered silver oxide was added to this mixture and stirred at reflux overnight. Silver salts were eliminated by filtration and the methoxyester acetonide was isolated in a pure form by evaporation of the solvent. No racemization on carbon 2 was observed during this step. Ethyl (2R,3R)-2-O-methyl-3,4-O-isopropylidene-3,4-dihydroxybutanoate **4a** and ethyl (2R,3S)-2-O-methyl-3,4-O-isopropylidene-3,4-dihydroxybutanoate **4b** were obtained in 95% and 97% yield.

To obtain the desired aldehydes, the general procedure adopted was to add the organic compound to 1:5 equiv. of DIBAH, both in toluene at −78°C. We chose a commercial toluene solution which is more stable than the usual THF or hexane solution.[11] The reduction of each of the two ester diastereomers by DIBAH under these experimental conditions provided the corresponding aldehydes in high yields, 95% for the 2-O-methyl-D-erythrose acetonide **5a** and 97% for the 2-O-methyl-L-threose acetonide **5b**.

Deprotection of the acetonide group with an acid resin in aqueous solution permitted 2-O-methyl-D-erythrose **1a** and 2-O-methyl-L-threose **1b** to be obtained. Free aldehydes were not isolated and the solution was used directly for enzymatic assays and for NMR studies. So, the development of this simple



Scheme 1. (a) (i) $CuSO_4$, dry acetone. (ii) H_2O_2, K_2CO_3, H_2O, 20°C then EtI, refluxing CH_3CN. (b) MeI, HgO_2, CH_3CN. (c) DIBAL-H, toluene. (d) Resin H^+, H_2O. (e) TsCl, Et_3N, DMAP, CH_2Cl_2. (f) LiCl, DMF. (g) Pd/C (10%), Et_3N, MeOH

asymmetric synthetic route using D-isoascorbic and L-ascorbic acids as starting materials has allowed us to isolate two enantiomerically pure aldehydes of the desired configuration.

2.2. *Syntheses of 2-deoxy-*D*-and* L*-erythrose **2a** and **2b** and the corresponding acetonides **7a** and **7b***

2.2.1. *From* D*-isoascorbic and* L*-ascorbic acids*

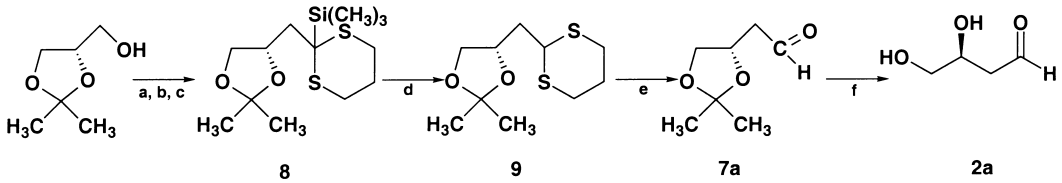
In this procedure,[12] the hydroxyesters **3a** and **3b** were respectively converted into the crystalline tosylates by treatment with *p*-toluenesulfonyl chloride in pyridine. The tosylate, when heated at 85°C with lithium chloride in dimethylformamide, gave a mixture of *erythro* and *threo* chloroesters. The diastereomeric mixture was subjected, without separation, to hydrogenolysis with 10% palladium on carbon in the presence of triethylamine. The ester, thus obtained in excellent yield, was reduced with DIBAH in toluene as described before for the methoxy esters to afford the aldehyde alone.

Following this sequence of reactions, D-isoascorbic acid was converted into the 2-deoxy-D-erythrose acetonide **7a** in an overall yield of 31% and L-ascorbic acid was converted into the 2-deoxy-L-erythrose acetonide **7b** in an overall yield of 62%.

The two free aldehyde enantiomers, 2-deoxy-D- and L-erythrose, **2a** and **2b**, have been obtained in aqueous solution by hydrolysis in the presence of acid resin (DOWEX WX8).

2.2.2. *From C_3 synthon (S)-solketal*

This method consists of the synthesis of a chiral dithiane, 2-[(2S)-2,3-O-isopropylidene-2,3-dihydroxypropyl]-1,3-dithiane **9**. This compound was already synthesized from L-malic acid by Mori et al.[13] and used as a chiral synthon in various polyol syntheses. We thought that it could be more easily prepared from the commercially available (S)-solketal. The aldehyde group can be introduced by use of the cyclic 2-lithio-1,3-dithiane which acts as a formyl anion equivalent (Scheme 2).



Scheme 2. (a) TsCl, Et_3N, $CHCl_3$, 85%. (b) NaI, methylethylketone, 75%. (c) 2-TMS-1,3-dithiane, n-BuLi, THF, 84%. (d) TBAF, THF, 67%. (e) CH_3I, acetone, 71%. (f) Resin H^+, H_2O

The (S)-solketal was first converted into the known (S)-tosylate[14] with tosyl chloride in triethylamine in 85% yield. The corresponding iodide was then obtained from tosylate by treatment with sodium iodide in acetone[15] in 75% yield. The iodide was transformed into the 1,3-dithiane via a trimethylsilyl compound:[16] the coupling of a trimethylsilyl-1,3-lithiodithiane at −25°C for 2 h with iodide gave the adduct **8** in 84% yield. The trimethylsilyl group was then eliminated by action of tetrabutylammonium fluoride in THF. The thioacetal was converted into the parent aldehyde by reaction with methyl iodide in moist acetone under reflux with a 71% yield. Thus, 2-deoxy-D-erythrose acetonide **7a** has been prepared from (S)-solketal by a five step procedure in 25% overall yield. The hydrolysis of the 2-deoxy-D-erythrose acetonide **7a** in the presence of an acid resin in aqueous solution gave the corresponding free aldehyde, the 2-deoxy-D-erythrose **2a**.

3. Conformational study

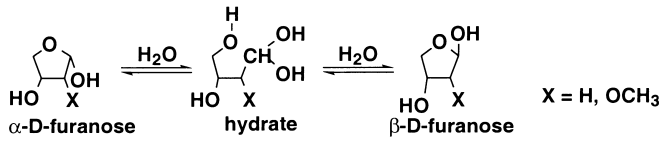
L-Threose and D-erythrose analogues and their corresponding acetonides prepared following the previous procedures were assayed as substrates for transketolase[5] and FB-aldolase. Even though the activities of FB-aldolase towards the substrates were high enough to allow the synthesis of rare heptulose-1-phosphates of D and L series, all substrates present high K_m values and suffer from low reactivity and we did not succeed in carrying out TK catalyzed syntheses. The hindrance of the dioxolane ring could explain the low reactivity of the acetonides. The case of unprotected substrates **1** and **2** is different. These compounds are capable of existing in aqueous solution in several forms in equilibrium: free aldehyde, hydrated aldehyde, and two hemiacetal anomers. Since TK reaction needs an aldehyde to be realized, it has seemed necessary to us to measure the percentage of cyclic and acyclic forms present in aqueous solution in the cases of 2-deoxy-D- and L-erythrose and for 2-O-methyl-D-erythrose and 2-O-methyl-L-threose. Such a study has already been done by Seriani et al. for 2-deoxy-D-erythrose.[6]

The proportion of cyclic (α and β furanoses) and acyclic (aldehyde and hydrate) forms were determined by ^1H and ^{13}C NMR spectroscopy. The chemical shifts of the deoxy and methoxy substituted furanoses in D_2O at 25°C are given in Table 1.

For the 2-deoxy-D- and L-erythrose, in the cyclic form, the β-configuration was attributed to the major tautomer on the basis of the results of Seriani. Our results are in agreement with his study. For the methoxy compounds, the α/β configuration was attributed by noting that, in all aldofuranose rings studied to date,[6] the C-1 signal of the anomer having O-1 and O-2 *trans* (β form) resonates downfield of the C-1 signal of its anomeric partner having O-1 and O-2 *cis* (α form).

One notices that according to ^1H and ^{13}C NMR spectra the free aldehyde form is undetectable. The percentages of each form present in aqueous solution have been calculated by quantitative ^{13}C NMR spectroscopy in D_2O at 25°C and are given in Table 2, together with literature data for D-erythrose and threose.

Table 1
^{1}H and ^{13}C NMR shifts of 2-deoxy-D- and L-erythrose **2a** and **2b**, 2-O-methyl-D-erythrose **1a** and 2-O-methyl-L-threose **1b** in D_2O at 25°C



Compound	Tautomeric form	C-1	C-2	C-3	C-4	O-CH_3	H-1
2a	2-désoxy-α-D-erythrose	99.08	42.19	71.04	75.17	/	5.57
	2-désoxy-β-D-erythrose	99.24	43.02	72.18	74.55	/	5.75
	2-désoxy-D-erytrose hydrate	89.85	41.51	69.84	66.66	/	5.27
1a	2-methoxy-α-D-érythrose	96.58	85.72	74.07	71.67	59.03	5.36
	2-methoxy-β-D-érythrose	100.45	88.67	73.82	75.32	57.71	5.45
	2-methoxy-D-érythrose hydrate	/	/	/	/	/	/
1b	2-methoxy-α-L-érythrose	97.78	88.30	75.36	72.93	60.56	5.41
	2-methoxy-β-L-érythrose	102.74	93.02	74.99	75.55	59.84	5.60
	2-methoxy-L-érythrose hydrate	/	/	/	/	/	/

Table 2
Behavior of 2-deoxy-D- and L-erythrose **2a** and **2b**, 2-O-methyl-D-erythrose **1a** and 2-O-methyl-L-threose **1b** in aqueous (D_2O) solution

	α form	β form	α/β	acyclic form
2-désoxy-D-erythrose	22.6 %	61.7 %	0.36	15.7 %
D-erythrose[6]	25.0 %	63.0 %	0.40	10.0 %
D-threose[6]	51. 8 %	37.6 %	1.38	9.6 %
2-methoxy-D-érythrose	29.6 %	70.4 %	0.42	/
2-methoxy-L-érythrose	30.1 %	69.9 %	0.43	/

For erythrose derivatives, the β form predominates and the presence of a substituent in position 2 decreases the proportion of the acyclic form which becomes undetectable for 2-methoxy compounds.

This phenomenon of cyclisation, in aqueous solution, of the tetroses synthesized, could explain their poor activities towards transketolase since the concentrations of the actual substrates (free aldehydic form) is small, very inferior to the K_m values, so that the reactions rates are low. The case of natural substrates like ribose-5-phosphate, which also exists mainly in a hemiacetal form, is probably different as the open form could be specifically stabilized in the active site of the enzyme.

In summary, the enantiomerically pure 2-O-methyl-L-threose and 2-O-methyl-D-erythrose and the

corresponding acetonides were, for the first time, efficiently synthesized from commercially available D-isoascorbic and its C_5 epimer, L-ascorbic acid. Both enantiomers of 3,4-dihydroxybutanal were also obtained from the same acids as well as the 3S enantiomer from enantiomerically pure solketal. These four enantiomerically pure tetrose analogues are interesting synthons for enzymatic or chemical syntheses. In addition, the NMR study has shown that, in the aldofuranose system, 2-O-methylation greatly enhances the proportion of the cyclic hemiacetal forms in aqueous solution.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were generally obtained in $CDCl_3$ at 100 and 400 MHz, respectively, on an AC400 Brucker spectrometer. Chemical shifts are expressed in ppm from tetramethylsilane (using as a reference residual $CHCl_3$). Optical rotations were measured on a Perkin–Elmer 141 spectropolarimeter. Mass spectra were performed on a VGMM 305 spectrometer. We did not observe, for all compounds synthesized owning an acetonide group, the molecular ion (M^+). The values obtained for these componds corresponded to the immediate fragmentation of a methyl group and so we will give ($M-CH_3$) values. For flash chromatography, silica gel GEDURAN SI 60 (0.040–0.063 mm, Merck) was employed while TLC analyses were performed on silica gel plates (Kieselgel 60 PF).

*4.2. Ethyl (2R,3R)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate **3a***

A mechanically stirred suspension of 50 g (284 mmol) of D-isoascorbic acid in acetone (250 ml) was treated with 90 g of anhydrous $CuSO_4$. After the reaction was stirred at room temperature for 24 h, a second 90 g portion of $CuSO_4$ was added, and stirring was continued for an additional 24 h. The reaction mixture was then filtered and concentrated, giving a near-quantitative yield of 3,4-O-isopropylidene-D-isoascorbic acid. The isopropylidene derivative was then dissolved in water (300 ml) containing 100 g of K_2CO_3. This solution was chilled in an ice bath and stirred while 30% H_2O_2 (87 ml) was slowly added. During the addition, the temperature was maintained below 20°C. The solution was stirred overnight and then concentrated in vacuo. The moist solid was extracted with boiling absolute EtOH. After filtration and evaporation, the salt was dried under vacuum to provide 62 g of material. Treatment of a mechanically stirred suspension of the salt with EtI (30 ml) in CH_3CN (400 ml) at reflux for 24 h gave, after concentration and removal of the inorganic salt, the crude ester **3a**: 28.69 g (50% from D-isoascorbic); $[\alpha]_D^{25}=-23.6$ (c 3.9, $CHCl_3$); (lit.[8] $[\alpha]_D=-29.14$ (c 156, MeOH)); MS, 189 ($M-CH_3$). ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J_{vic}=7.1 Hz); 1.23 (s, 3H); 1.31 (s, 3H); 3.47 (d, 1H, OH, J=5.7 Hz); 3.92 (dd, 1H, J_{gem}=7.2 Hz, J_{vic}=6.3 Hz); 4.01 (dd, 1H, J_{gem}=7.3 Hz, J_{vic}=6.5 Hz); 4.03 (dd, 1H, J_{gem}=7.2 Hz, J_{OH}=5.7 Hz); 4.14 (q, 2H, J_{vic}=7.2 Hz); 4.20 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.13 (C_7); 25.10 and 26.34 (C_a and C_b); 61.89 (C_6); 65.04 (C_2); 71.09 (C_4); 76.78 (C_3); 109.95 (C_5); 172.07 (C_1).

*4.3. Ethyl (2R,3S)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate **3b***

From L-ascorbic acid using the above procedure: 46.35 g (80% from L-isoascorbic); $[\alpha]_D^{25}=+16.6$ (c 2.9, $CHCl_3$); MS, 189 ($M-CH_3$). ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, J_{vic}=7.1 Hz); 1.23 (s, 3H); 1.30 (s, 3H); 3.18 (d, 1H, OH, J=7.9 Hz); 3.94 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=7.0 Hz); 4.01 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=7.0 Hz); 4.04 (dd, 1H, J_{gem}=3.2 Hz, J_{OH}=8.0 Hz); 4.18 (q, 2H, J_{vic}=7.0 Hz); 4.30 (m, 1H). ^{13}C NMR

($CDCl_3$) δ 14.13 (C_7); 25.34 and 26.08 (C_a and C_b); 61.94 (C_6); 65.62 (C_2); 70.32 (C_4); 76.37 (C_3); 109.92 (C_5); 172.10 (C_1).

4.4. Ethyl (2R,3R)-2-O-methyl-3,4-O-isopropylidene-3,4-dihydroxybutanoate **4a**

Compound **3a** (2 g, 9.8 mmol) was dissolved in CH_3CN (60 ml) and CH_3I (20 ml). The mixture was stirred at reflux overnight with Ag_2O (3.6 g). Methylation was complete based on TLC (silica gel, $CHCl_3$). The solids were removed by filtration and the filtrate concentrated to dryness to give the methyl ester **4a**: 2.0 g (95%); $[\alpha]_D^{25}=-1.6$ (c 3.6, $CHCl_3$); MS, 203 ($M-CH_3$). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J_{vic}=7.1 Hz); 1.27 (s, 3H); 1.31 (s, 3H); 3.40 (s, 3H); 3.75 (dd, 1H, J_{gem}=8.3 Hz, J_{vic}=5.9 Hz); 3.81 (d, 1H, J_{vic}=6.3 Hz); 3.98 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=6.3 Hz); 3.90 (q, 2H, J_{vic}=7.2 Hz); 4.31 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.01 (C_7); 25.37 and 26.13 (C_a and C_b); 58.51 (C_8); 60.76 (C_6); 65.96 (C_2); 77.10 (C_4); 81.28 (C_3); 109.75 (C_5); 170.89 (C_1).

4.5. Ethyl (2R,3S)-2-O-methyl-3,4-O-isopropylidene-3,4-dihydroxybutanoate **4b**

From **3b** using the above procedure was afforded **4b**: 2.1 g (97%); $[\alpha]_D^{25}=+0.4$ (c 1.54, $CHCl_3$); MS, 203 ($M-CH_3$). ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J_{vic}=7.1 Hz); 1.25 (s, 3H); 1.32 (s, 3H); 3.40 (s, 3H); 3.98 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=6.3 Hz); 4.01 (d, 1H, J_{vic}=6.1 Hz); 4.05 (dd, 1H, J_{gem}=8.0 Hz, J_{vic}=6.7 Hz); 4.11 (q, 2H, J_{vic}=7.1 Hz); 4.47 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.13 (C_7); 25.20 and 26.26 (C_a and C_b); 58.72 (C_8); 61.16 (C_6); 65.42 (C_2); 75.67 (C_4); 81.58 (C_3); 109.81 (C_5); 169.79 (C_1).

4.6. (2R,3R)-2-O-Methyl-3,4-O-isopropylidene-3,4-dihydroxybutanal **5a**

Compound **4a** (1.6 g, 8.5 mmol) was dissolved in dry toluene (53 ml). The solution was maintained under nitrogen and cooled to −78°C. A quantity (8.6 ml, 1.5 equiv.) of 1.5 M DIBAL-H solution in toluene was introduced into the flask. After 15 min, 25 ml of methanol was added and the solution was slowly warmed to room temperature. A sodium potassium tartrate saturated solution (2 ml), 4 ml of brine and 70 ml of AcOEt were added with $MgSO_4$. After 1 h, the solids were removed by filtration and the filtrate concentrated to dryness to give the aldehyde **5a**: 1.2 g (97%); $[\alpha]_D^{25}=+2.1$ (c 5.3, $CHCl_3$); MS, 159 ($M-CH_3$). ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H); 1.40 (s, 3H); 3.43 (s, 3H); 3.55 (dd, 1H, J_{vic}=2.0 Hz, J_{vic}=6.1 Hz); 3.90 (dd, 1H, J_{gem}=8.7 Hz, J_{vic}=5.3 Hz); 4.03 (dd, 1H, J_{gem}=8.6 Hz, J_{vic}=6.3 Hz); 4.23 (m, 1H); 9.68 (d, 1H, J_{vic}=2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 24.97 and 26.33 (C_a and C_b); 58.75 (C_8); 65.72 (C_2); 74.71 (C_4); 85.26 (C_3); 109.49 (C_5); 201.14 (C_1).

4.7. (2R,3S)-2-O-Methyl-3,4-O-isopropylidene-3,4-dihydroxybutanal **5b**

From **4b** using the above procedure was afforded **5b**: 1.2 g (97%); $[\alpha]_D^{25}=-4.1$ (c 4.1, $CHCl_3$); MS, 159 ($M-CH_3$). ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H); 1.35 (s, 3H); 3.45 (s, 3H); 3.58 (dd, 1H, J_{vic}=2.1 Hz, J_{vic}=6.3 Hz); 3.90 (dd, 1H, J_{gem}=8.7 Hz, J_{vic}=5.5 Hz); 4.06 (dd, 1H, J_{gem}=8.5 Hz, J_{vic}=5.9 Hz); 4.28 (m, 1H); 9.60 (d, 1H, J_{vic}=2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 24.56 and 26.23 (C_a and C_b); 58.35 (C_8); 65.67 (C_2); 75.03 (C_4); 84.95 (C_3); 110.10 (C_5); 201.65 (C_1).

4.8. (S)-3,4-O-Isopropylidene-3,4-dihydroxybutanal **7a**

From the 2-deoxyester **6a** using the above procedure was afforded **7a**: 1.2 g (97%); $[\alpha]_D^{25}$=+8.3 (c 1.3, $CHCl_3$); (lit.[17] $[\alpha]_D^{24}$=+16.5 (c 5.32, $CHCl_3$)); MS, 129 (M−CH_3). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H); 1.37 (s, 3H); 2.65 (ddd, 1H, J_{gem}=15.3 Hz, J_{vic}=7.1 Hz, J_{vic}=2.0 Hz); 2.85 (ddd, 1H, J_{gem}=15.7 Hz, J_{vic}=6.7 Hz, J_{vic}=2.1 Hz); 3.60 (dd, 1H, J_{gem}=8.3 Hz, J_{vic}=7.1 Hz); 4.15 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=6.3 Hz); 4.41 (m, 1H); 9.80 (d, 1H, J_{vic}=2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 25.15 and 25.78 (C_a and C_b); 47.56 (C_2); 68.80 (C_4); 71.53 (C_3); 109.28 (C_5); 198.98 (C_1).

4.9. (R)-3,4-O-Isopropylidene-3,4-dihydroxybutanal **7b**

From the 2-deoxyester **6b** using the above procedure was afforded **7b**: 1.2 g (97%); $[\alpha]_D^{25}$=−7.9 (c 2.9, $CHCl_3$); MS, 129 (M−CH_3). ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H); 1.37 (s, 3H); 2.62 (ddd, 1H, J_{gem}=15.1 Hz, J_{vic}=6.7 Hz, J_{vic}=2.0 Hz); 2.83 (ddd, 1H, J_{gem}=15.0 Hz, J_{vic}=5.9 Hz, J_{vic}=2.1 Hz); 3.56 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=7.0 Hz); 4.08 (dd, 1H, J_{gem}=8.0 Hz, J_{vic}=6.5 Hz); 4.47 (m, 1H); 9.80 (d, 1H, J_{vic}=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.40 and 26.75 (C_a and C_b); 47.79 (C_2); 69.10 (C_4); 70.61 (C_3); 109.20 (C_5); 200.01 (C_1).

4.10. 2-[(2S)-2,3-O-Isopropylidene-2,3-dihydroxypropyl]-2-trimethylsilyl-1,3-dithiane **8**

2-Trimethylsilyl-1,3-dithiane (4.6 g, 24 mmol) was dissolved in dry THF. The solution was maintained under nitrogen and cooled to −40°C. A quantity (1.5 g, 24 mmol) of 1.5 M n-butyllithium solution in hexane was introduced into the flask and the mixture was stirred for 2 h at −25°C. Then the solution was cooled to −78°C and (R)-2,2-dimethyl-4-(iodomethyl)-1,3-dioxan (5.8 g, 24 mmol) was added. The solution was stirred for 3 h at −78°C and slowly warmed to room temperature. After 24 h, 370 ml of H_2O were added and the aqueous layer was treated with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give **8**: 6.2 g (84%); $[\alpha]_D^{25}$=−2.1 (c 2.2, $CHCl_3$); MS, 291 (M−CH_3). ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9H); 1.25 (s, 3H); 1.39 (s, 3H); 2.01 (dd, 2H, J_{gem}=8.1 Hz, J_{vic}=4.4 Hz); 2.68 (*pseudo* t, 2H, J_{vic}=4.0 Hz); 2.83 (*pseudo* t, 2H, J_{vic}=4.3 Hz); 2.96 (m, 2H); 3.25 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=5.9 Hz); 3.56 (dd, 1H, J_{gem}=8.3 Hz, J_{vic}=6.7 Hz); 4.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.14 and 25.63 (C_a and C_b); 26.83 (C_5); 29.88 ($3CH_3$); 30.01 and 30.51 (C_4 and C_6); 34.03 (C_2); 38.70 ($C_{6'}$); 70.20 ($C_{5'}$); 75.60 ($C_{4'}$); 110.37 ($C_{2'}$).

4.11. 2-[(2S)-2,3-O-Isopropylidene-2,3-dihydroxypropyl]-1,3-dithiane **9**

To a solution of **8** (5 g, 16.3 mmol) in 300 ml of dry THF was added 2 ml of tetrabutylammonium fluoride. The solution was stirred for 6 h at room temperature and then extracted with AcOEt. The organic layer was washed with H_2O and brine and then dried over $MgSO_4$. The solvent was removed and the residue submitted to flash chromatography (pentane:ether=80:20) to give **9**: 3.0 g (67%); $[\alpha]_D^{25}$=−9.3 (c 5.1, $CHCl_3$); (lit.[18] $[\alpha]_D^{23}$=−9.05, $CHCl_3$); MS, 259 (M−CH_3). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H); 1.37 (s, 3H); 1.99 (dd, 2H, J_{gem}=8.3 Hz, J_{vic}=4.3 Hz); 2.76 (*pseudo* t, 2H, J_{vic}=4.1 Hz); 2.80 (*pseudo* t, 2H, J_{vic}=4.3 Hz); 2.88 (m, 2H); 3.53 (dd, 1H, J_{gem}=8.2 Hz, J_{vic}=6.4 Hz); 4.05 (dd, 1H, J_{gem}=8.1 Hz, J_{vic}=6.3 Hz); 4.15 (dd, 1H, J_{gem}=9.4 Hz, J_{vic}=4.2 Hz); 4.34 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.64 and 25.78 (C_a and C_b); 27.04 (C_5); 29.40 and 30.16 (C_4 and C_6); 30.39 (C_2); 39.96 ($C_{6'}$); 69.24 ($C_{5'}$); 72.59 ($C_{4'}$); 109.09 ($C_{2'}$).

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