4-*O*-Benzyl-2,3-*O*-isopropylidene-D-erythrose and -D-threose from 2,3-*O*-Isopropylidene-D-glyceraldehyde via Thiazole Intermediates. Synthesis of 2-Deoxykanosamine

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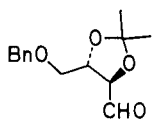
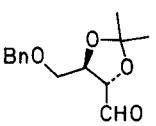
The adduct derived from 2,3-*O*-isopropylidene-D-glyceraldehyde and 2-(trimethylsilyl)thiazole is readily converted into the title D-erythrose (50% overal yield) by selective protection of the hydroxy groups and cleavage of the thiazole ring; the D-threose derivative is obtained from the former by base-catalyzed epimerization at C-2. Wittig olefination of the D-erythrose derivative followed by Michael addition of benzylamine and aldehyde liberation from the thiazole ring leads to the amino sugar 2-deoxykanosamine (methyl 6-*O*-benzyl-3-benzylamino-2,3-dideoxy-α-D-arabinopyranoside) in 50% overall yield.

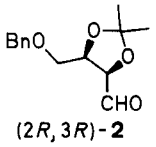
Chiral C_3 and C_4 polyalkoxy aldehydes[1-2] occupy a prominent position in the arsenal of synthetic building blocks because they are effective precursors to numerous compounds of biological relevance such as natural and unnatural sugars and various families of macrolide antibiotics.[3] Quite often, the successful implementation of synthetic strategies employing these chiral educts, rely on the differentiation between the various hydroxy groups by a suitable protecting group arrangement. Various aldehydes of this type can be prepared by functional group elaborations of natural sugars. Typically, a five-step route to 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose [(2*R*,3*S*)-**1**] and its enantiomer *ent*-**1** (Mukaiyama aldehydes) from (*R*,*R*)- and (*S*,*S*)-tartaric acid, respectively, has been described and the utility of these compounds in the synthesis of monosaccharides has been amply demonstrated.[4] The same strategy cannot be applied to the synthesis of the protected D-erytrose (*R*,*R*)-**2** or its enantiomer *ent*-**2** from *meso*-tartaric acid unless asymmetrization of the sequence is achieved by chemical or enzymatic means.[5] Consequently, a rather long route leading to **2** and *ent*-**2** was developed involving Sharpless asymmetric epoxidation as a key step.[6] This route however did not appeal to us for the multigram preparation of **2** which we need as a chiral C_4 building block for the synthesis of various carbohydrate structures which are underway in our laboratory.[7] We describe here a convenient route to (*R*,*R*)-**2** and its conversion to *ent*-**1** from the readily available 2,3-*O*-isopropylidene-D-glyceraldehyde[1,8] [(*R*)-**3**] via thiazole intermediates serving as masked aldehydes.[9] The same protocol should be amenable to the preparation of the stereoisomers *ent*-**2** and (*R*,*S*)-**1** starting from L-glyceraldehyde.[1]



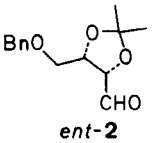
(2*R*, 3*S*)-**1**



ent-**1**



(2*R*, 3*R*)-**2**

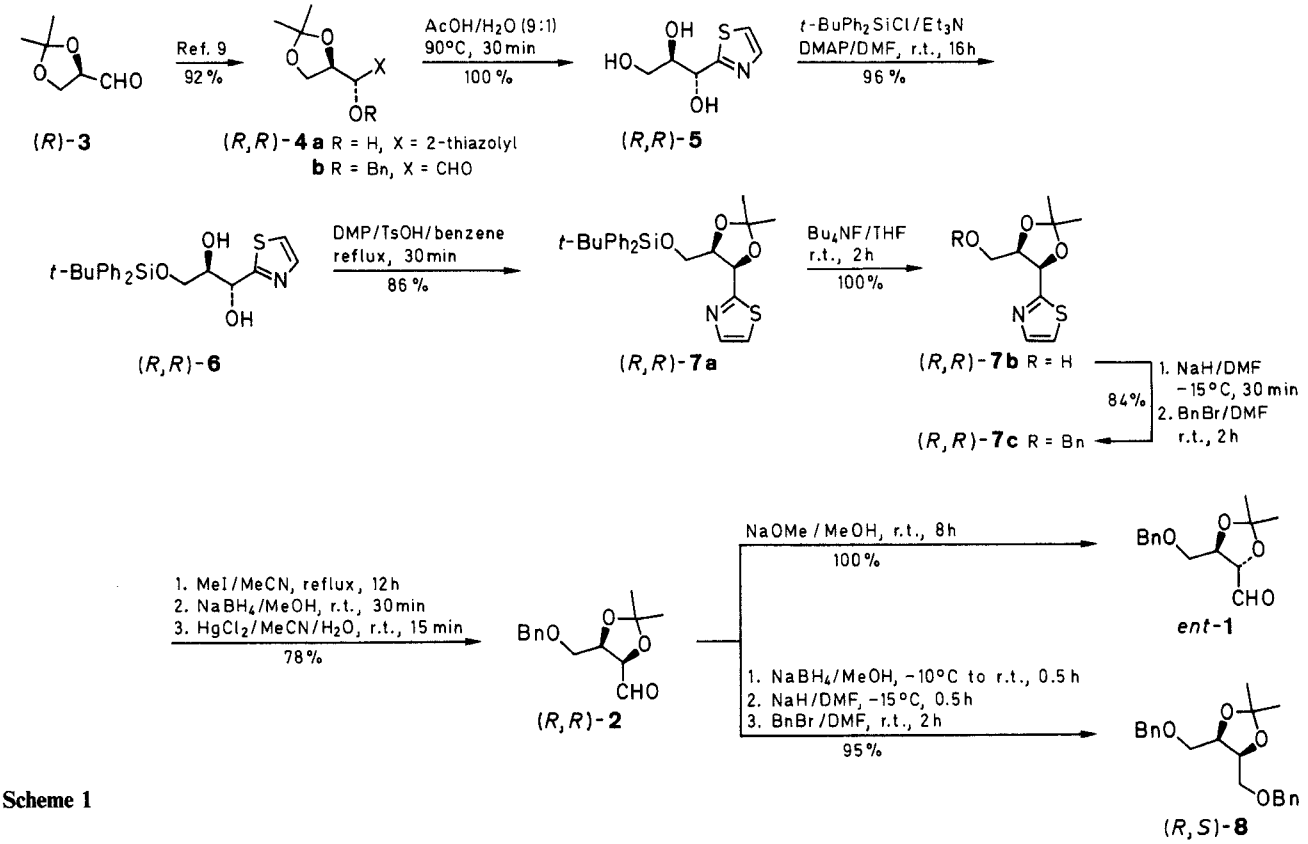


ent-**2**

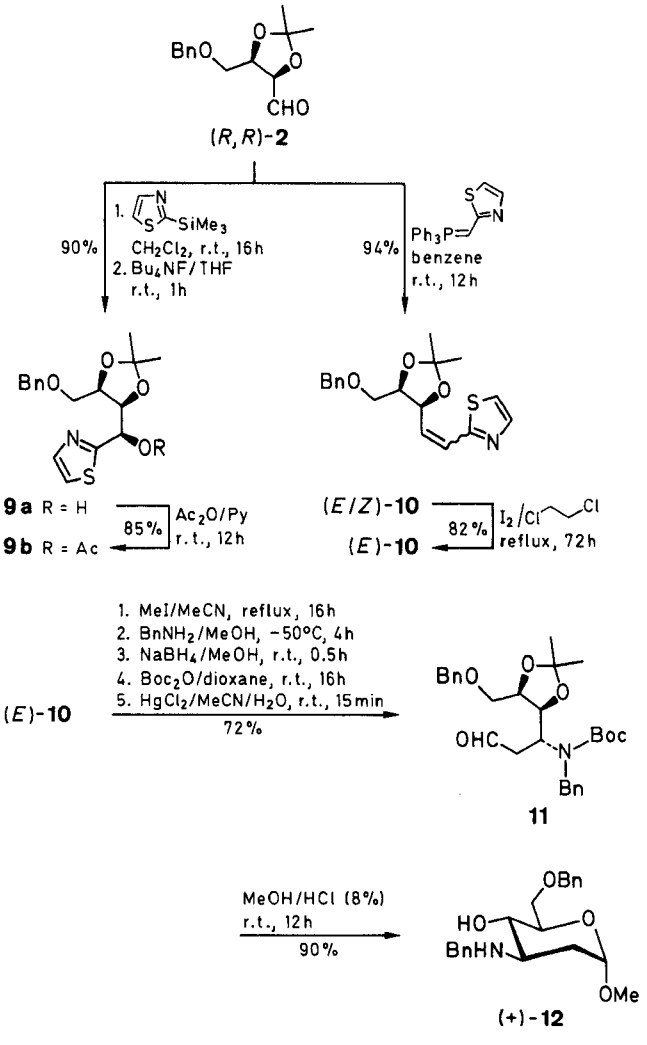
The key intermediate, α-hydroxyalkylthiazole (*R*,*R*)-**4a** (Scheme 1), was available in multigram quantities by *anti*-diastereoselective addition (ds ≥ 95%) of 2-(trimethylsilyl)thiazole, 2-TST, to (*R*)-**3** as described.[10] It is worth mentioning that *O*-benzylation of **4a** and liberation of the aldehyde from the thiazole ring affords[10] the D-erythrose derivative **4b** having the same protecting hydroxy groups as **2** but with a different distribution. Cleavage of the 1,3-dioxolane ring in **4a** provided the triol (*R*,*R*)-**5** which was temporarily protected as the *O*-silyl derivative **6**. This compound was readily converted via the intermediates **7a** and **7b** to the *O*-benzyl derivative **7c** having the hydroxy group protected as in (*R*,*R*)-**2**. The very mild conditions employed for the benzylation of **7b** to **7c** prevented appreciable (^{1}H NMR) epimerization at the α-position to the thiazole ring. A shorter route to the intermediate **7c** by benzylation of **5** appeared impractical since this reaction occurred preferentially at the secondary hydroxy group adjacent to the thiazole ring rather than at the primary hydroxy group. The aldehyde liberation in **7c** by the usual thiazole-to-formyl deblocking sequence[10] gave the desired compound (*R*,*R*)-**2** in 50% overall yield from **3**. The conversion of **2** into the symmetrically substituted *meso*-erythritol **8**, supports the *anti*-configuration across the 1,2-diol system. Compound **2** proved to be configurationally stable on standing at room temperature for one week but treatment with catalytic sodium methoxide in methanol effected smooth epimerization at C-2 providing the more stable diastereomer *ent*-**1** in quantitative yield.[11] The essential role of acetonide protection in the latter reaction has been already discussed.[5] This new synthesis of *ent*-**1** which ultimately makes use of D-mannitol as the commercially available precursor to (*R*)-**3**, offers an alternative to the Mukaiyama route[4] via the rather expensive (*S*,*S*)-tartaric acid.

The aldehyde **2** has proven to be a useful intermediate toward polyoxygenated alkyl and alkenylthiazole precursors to carbohydrates (Scheme 2). The addition of 2-TST to **2** ocurred with a good level of diastereoselectivity (ds = 90%) to give the alcohol *anti*-**9a** (Felkin-Anh adduct) as major product which was isolated and characterized as the ester **9b**. The configuration of the adduct **9a** was assigned by analogy of structures derived from the addition of 2-TST to various α,β-dialkoxyaldehydes where *anti*-selectivity was observed as a rule.[9] It is worth pointing out that addition of 2-TST to **2** was in no instances plagued by the formation of side-products as observed[10] in the reaction of 2-TST with the isomer 2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythrose **4b**.

The Wittig reaction of **2** with [(2-thiazolyl)methylene]triphenylphosphorane,[12] 2-TMP, in benzene afforded a 94% yield of the alkenylthiazole **10** as a 57 : 43 mixture of *E*/*Z*-isomers according to ^{1}H NMR. Upon



Scheme 1



Scheme 2

reflux of the mixture in 1,2-dichloroethane in the presence of iodine, the *E*/*Z*-ratio became 90 : 10. After chromatographic separation from the minor isomer, the pure alkene (*E*)-**10** was subjected to the one-pot Michael addition of benzylamine and aldehyde liberation sequence[13] to give the protected chiral amino hexanal **11** in 72% overall yield. The *syn*-selectivity (ds = 93%) of the Michael addition was demonstrated by cyclization of **11** to the *O*-methyl pyranoside **12**, the ^{1}H NMR spectrum of which showed a rather large coupling constant (9.6 Hz) between H(3) and H(4) indicating a trans-diequatorial arrangement between the benzylamino and the hydroxy group. The structure of **12** corresponds to that of the 2-deoxy derivative of the amino sugar Kanosamine (3-amino-3-deoxy-D-glucopyranose) which is one of the sugar fragments isolated from the natural product *hikizimycin*,[14] a potent anthelmintic agent.

We expect the protected trialkoxyaldehyde (*R*,*R*)-**2** and its enantiomer *ent*-**2** to find various synthetic applications as new C_4 chiral building blocks in organic synthesis.

Melting points were taken using a Büchi apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Gemini 300 Varian spectrometer unless otherwise stated using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Model 297 grating spectrophotometer. Elemental analyses were performed on a Model 1106 microanalyzer (Carlo Erba). Optical rotations were measured at ca. 20 °C using a Perkin-Elmer Model 214 polarimeter. Thin layer chromatography (TLC) was performed on glass-slides precoated with silica gel (Merck Kiesel gel 60 F_{254}) and preparative chromatography on columns of silica gel (Merck 70–230 mesh). All experiments were carried out with freshly distilled and dried solvents.

(1*R*,2*R*)-1-(2-Thiazolyl)-1,2,3-propanetriol (5):
(1*R*,2*R*)-2,3-*O*-Isopropylidene-1-(2-thiazolyl)-1,2,3-propanetriol[9] (**4a**; 5.0 g, 23.3 mmol) was treated with 90% aq AcOH (30 mL) at 90°C for 30 min. The solution was concentrated under reduced pressure. The residue was treated with benzene (30 mL) and distilled in vacuo (five cycles). The crude product was placed under reduced pressure to remove traces of residual solvent to give (*R*,*R*)-**5** as a white solid; yield: 4.08 g (100%); mp 86–88°C; $[\alpha]_D^{20} = +9.5°$ (*c* = 1.09, MeOH).

$C_6H_9NO_3S$	calc.	C 41.13	H 5.18	N 7.99
(175.2)	found	41.43	4.86	8.13

^{1}H NMR (D_2O): δ = 3.42 (dd, 1 H, *J* = 11.9, 6.8 Hz), 3.54 (dd, 1 H, *J* = 11.9 Hz, 3.6 Hz), 3.85 (ddd, 1 H, *J* = 6.8, 5.6, 3.5 Hz), 4.86 (d, 1 H, *J* = 5.6 Hz), 7.38 (d, 1 H, *J* = 3.3 Hz), 7.59 (d, 1 H, *J* = 3.3 Hz).

^{13}C NMR (D_2O): δ = 67.95, 77.46, 80.35, 126.96, 148.18, 178.84.

(1*R*,2*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1-(2-thiazolyl)-1,2,3-propanetriol (6):
To a well-stirred solution of triol (*R*,*R*)-**5** (4.0 g, 22.8 mmol) in DMF (25 mL), Et_3N (2.43 g, 3.37 mL, 24.0 mmol), 4-dimethylaminopyridine (DMAP) (0.11 g, 0.9 mmol) and *tert*-butyldiphenylsilyl chloride (6.6 g, 24.0 mmol) were added and stirring was maintained at 25°C for 16 h. The mixture was poured into H_2O (150 mL) and extracted with EtOAc (3 × 75 mL). The organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed by distillation, and the residue was passed rapidly through a short column of silica gel with 20% hexane in Et_2O as eluant to give (*R*,*R*)-**6** as a colorless oil; yield: 9.1 g (96%); $[\alpha]_D^{20} + 2.5°$ (*c* = 0.52, $CHCl_3$).

$C_{22}H_{27}NO_3SSi$	calc.	C 63.89	H 6.58	N 3.39
(413.6)	found	64.05	6.79	3.43

^{1}H NMR ($CDCl_3 + D_2O$): δ = 1.10 (s, 9 H), 3.84 (dd, 1 H, *J* = 10.5, *J* = 5.7 Hz), 3.95 (dd, 1 H, *J* = 10.5, 4.6 Hz), 4.03 (ddd, 1 H, *J* = 6.5, 5.7, 4.6 Hz), 5.10 (d, 1 H, *J* = 6.5 Hz), 7.40 (m, 7 H), 7.65 (m, 4 H), 7.74 (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3 + D_2O$): δ = 18.18, 25.90 (3C), 64.95, 72.57, 72.71, 118.81, 127.25 (2C), 127.47 (2C), 129.59 (2C), 132.23 (2C), 135.21 (2C), 135.49 (2C), 141.87, 162.38.

(1*R*,2*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-1-(2-thiazolyl)-1,2,3-propanetriol (7a):
A solution of diol (*R*,*R*)-**6** (9.0 g, 21.8 mmol), 2,2-dimethoxypropane (DMP) (5.3 mL, 43.6 mmol), and TsOH (60 mg, 0.32 mmol) in benzene (130 mL) was refluxed for 30 min, then slowly distilled until a volume of 100 mL of solvent had been collected. Additional DMP (1.5 mL, 12.3 mmol) and benzene (60 mL) were added, and the procedure was repeated, collecting 50 mL of distillate. The cooled mixture was partitioned between sat. aq $NaHCO_3$ (60 mL) and pentane (300 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/Et_2O, 90 : 10) to give (*R*,*R*)-**7a** as a colorless oil; yield: 9.4 g (86%); $[\alpha]_D^{20}$ − 3.1° (*c* = 0.96, $CHCl_3$).

$C_{25}H_{31}NO_6SSi$	calc.	C 59.86	H 6.23	N 2.79
(501.6)	found	59.80	6.18	3.01

^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 9 H), 1.48 (s, 3 H), 1.67 (s, 3 H), 3.42 (dd, 1 H, *J* = 11.2, 6.2 Hz), 3.68 (dd, 1 H, *J* = 11.2, 5.2 Hz), 4.61 (ddd, 1 H, *J* = 7.1, 6.2, 5.2 Hz), 5.61 (d, 1 H, *J* = 7.1 Hz), 7.26 (d, 1 H, *J* = 3.2 Hz), 7.37 (m, 6 H), 7.56 (m, 4 H), 7.70, (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 18.13, 23.91, 25.80 (3C), 26.20, 62.12, 76.23, 78.70, 109.38, 127.15 (4c), 129.17 (2C), 133.02, 133.15, 135.25 (2C), 135.30 (2C), 142.36, 169.04.

(1*R*,2*R*)-1,2-*O*-Isopropylidene-1-(2-thiazolyl)-1,2,3-propanetriol (7b):
A solution of (*R*,*R*)-**7a** (9.30 g, 18.5 mmol) in THF (100 mL) was treated with Bu_4NF 1 M solution in THF (20 mL, 20 mmol) at r.t. After 2 h, sat. aq $NaHCO_3$ (150 mL) was added and the mixture was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and distilled under reduced pressure. Purification of the crude product by column chromatography on silica gel (Et_2O/hexane, 60 : 40) gave pure (*R*,*R*)-**7b** as a colorless oil; yield: 3.98 g (~100%); $[\alpha]_D^{20}$ − 21.2° (*c* = 1.36, $CHCl_3$).

$C_9H_{13}NO_3S$	calc.	C 50.22	H 6.09	N 6.51
(215.3)	found	50.40	6.10	6.86

^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 3 H), 1.69 (s, 3 H), 3.31 (ddd, 1 H, *J* = 11.7, 8.6, 5.0 Hz), 3.70 (ddd, 1 H, *J* = 11.7, 10.0, 5.2 Hz), 4.04 (dd, 1 H, *J* = 10.0, 5.0 Hz, ex. D_2O), 4.71 (ddd, 1 H, *J* = 8.6, 6.8, 5.2 Hz), 5.54 (d, 1 H, *J* = 6.8 Hz), 7.35 (d, 1 H, *J* = 3.2 Hz), 7.81 (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 23.85, 26.24, 60.28, 76.91, 78.27, 110.08, 118.75, 142.62, 171.82.

(1*R*,2*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-1-(2-thiazolyl)-1,2,3-propanetriol (7c):
A well stirred suspension of NaH (60% dispersion in mineral oil, 0.76 g, 19 mmol) in DMF (30 mL) was cooled at − 15°C. Then a solution of the alcohol (*R*,*R*)-**7b** (3.9 g, 18.1 mmol) in DMF (20 mL) was added and stirring was maintained at − 15°C for 10 min. Benzyl bromide (3.25 g, 2.26 mL, 19 mmol) was added and the mixture was stirred at r.t. for 2 h. The mixture was poured into H_2O (150 mL) and extracted with hexane (5 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was chromatographed on silica gel (hexane/Et_2O 80 : 20) to give (*R*,*R*)-**7c** as a colorless oil; yield: 4.64 g (84%); $[\alpha]_D^{20}$ − 41.8° (*c* = 0.60, $CHCl_3$).

$C_{16}H_{19}NO_3S$	calc.	C 62.93	H 6.27	N 4.59
(305.4)	found	62.79	6.10	4.46

^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 3 H), 1.71 (s, 3 H), 3.10 (dd, 1 H, *J* = 10.5, 7.8 Hz), 3.50 (dd, 1 H, *J* = 10.5, 3.5 Hz), 4.34 (d, 1 H, *J* = 12.2 Hz), 4.49 (d, 1 H, *J* = 12.2 Hz), 4.75 (ddd, 1 H, *J* = 7.8, 7.2, 3.5 Hz), 5.52 (d, 1 H, *J* = 7.20 Hz), 7.29 (m, 6 H), 7.73 (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 23.78, 26.19, 68.55, 72.75, 76.06, 77.35, 109.87, 118.73, 127.17, 127.31, 127.89, 137.57, 142.47, 169.73.

4-*O*-Benzyl-2,3-*O*-isopropylidene-D-erythrose (*R*,*R*)-2:
A solution of (*R*,*R*)-**7c** (5.2 g, 17 mmol) in MeCN (50 mL) was treated with MeI (24.1 g, 170 mmol) and refluxed for 12 h. The solvent was distilled under reduced pressure. The residue was dissolved in MeOH (80 mL) and $NaBH_4$ (1.29 g, 34 mmol) was added portionwise. After 30 min of stirring at r.t. the solvent was distilled in vacuo and the residue was partitioned between brine (60 mL) and CH_2Cl_2 (150 mL). The organic layer was dried (Na_2SO_4) and rotatory evaporated. The residue was dissolved in MeCN (40 mL) and added to a solution of $HgCl_2$ (5.05 g, 18.7 mmol) in a 4 : 1 mixture of MeCN/H_2O (100 mL). After being stirred at r.t. for 15 min, the mixture was filtered through Celite and the filtrate was evaporated. The residue was treated with sat. aq KI (50 mL) and extracted with $CHCl_3$ (3 × 80 mL). The combined organic layers were washed with sat. aq KI, dried (Na_2SO_4), filtered and concentrated in vacuo. The pale-yellow oil was purified by column chromatography on silica gel (hexane/Et_2O, 80 : 20) to give the aldehyde (*R*,*R*)-**2** as a colorless oil; yield: 3.32 g (78%); $[\alpha]_D^{20}$ + 20.9° (*c* = 0.42, $CHCl_3$).

$C_{14}H_{18}O_4$	calc.	C 67.18	H 7.25	
(250.3)	found	67.10	7.43	

IR ($CHCl_3$): ν = 1730 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 3 H), 1.64 (s, 3 H), 3.53 (dd, 1 H, *J* = 10.7, 4.1 Hz), 3.70 (dd, 1 H, *J* = 10.7, 3.9 Hz), 4.47, (dd, 1 H, *J* = 7.9, 2.4 Hz), 4.50 (m, 2 H), 4.61 (ddd, 1 H, *J* = 7.9, 4.1, 3.9 Hz), 7.34 (m, 5 H), 9.67 (d, 1 H, *J* = 2.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 24.12, 26.03, 69.72, 72.77, 77.55, 80.21, 110.54, 127.34, 127.39, 128.03, 137.17, 200.31.

1,4-Di-*O*-Benzyl-2,3-*O*-isopropylidene-D-erythritol (8):
A solution of (*R*,*R*)-**2** (0.1 g, 0.4 mmol) in MeOH (10 mL) was treated with $NaBH_4$ (25 mg, 0.66 mmol) at − 10°C. After 30 min, acetone was added and the solvent was evaporated. Brine (10 mL)

was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The extract was dried (Na_2SO_4) and the solvent was concentrated in vacuo. The residue was dissolved in anhydr. DMF (5 mL) and added to a well-stirred suspension of NaH (60% dispersion in mineral oil, 18 mg, 0.45 mmol) in DMF (5 mL) at −15°C. After stirring for 10 min, benzyl bromide (0.77 g, 0.54 mL, 0.45 mmol) was added and the mixture was stirred at r.t. for 2 h. The mixture was poured into H_2O (25 mL) and extracted with hexane (5 × 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was chromatographed on silica gel (hexane/Et_2O, 80 : 20) to give (*R,S*)-**8** as a colorless oil; yield: 0.13 g (95%); $[\alpha]_D^{20}$ 0°.

$C_{21}H_{26}O_4$	calc.	C 73.66	H 7.65
(342.4)	found	73.81	7.30

^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 3H), 1.39 (s, 3H), 3.43 (dd, 2H, *J* = 10.1, 6.5 Hz), 3.52 (dd, 2H, *J* = 10.1, 5.1 Hz), 4.30 (dd, 2H, *J* = 6.5, 5.1 Hz), 4.42 (d, 2H, *J* = 12.2 Hz), 4.50 (d, 2H, *J* = 12.2 Hz), 7.25 (m, 10H).

^{13}C NMR ($CDCl_3$): δ = 24.38, 26.91, 68.02, 72.81, 75.25, 108.32, 127.30, 127.41, 128.00, 137.65.

4-*O*-Benzyl-2,3-*O*-isopropylidene-D-threose (*ent*-1):

A solution of (*R,R*)-**2** (0.5 g, 2 mmol) in MeOH (30 mL) is treated at r.t. with NaOMe (10 mg, 0.19 mmol) and stirring was maintained for 8 h. The solvent was distilled under reduced pressure and the residue was partitioned between sat. aq $NaHCO_3$ (30 mL) and $CHCl_3$ (30 mL). The organic layer was washed with brine dried (Na_2SO_4), filtered and concentrated in vacuo to give *ent*-**1** as an oil; yield: 0.5 g (~100%); $[\alpha]_D^{20}$ −15.6° (*c* = 1.48, $CHCl_3$).

$C_{14}H_{18}O_4$	calc.	C 67.18	H 7.25
(250.3)	found	67.29	6.91

IR ($CHCl_3$): $\nu = 1725\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 3H), 1.52 (s, 3H), 3.58 (m, 2H), 4.18 (dd, 1H, *J* = 7.3, 1.5 Hz), 4.21 (m, 1H), 4.53 (br s, 2H), 7.28 (m, 5H), 9.58 (d, 1H, *J* = 1.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.29, 25.91, 69.25, 72.98, 75.59, 81.45, 111.29, 127.30, 127.41, 128.06, 135.21, 200.59.

(1*R*,2*R*,3*R*)-4-*O*-Benzyl-2,3-*O*-isopropylidene-1-(2-thiazolyl)-1,2,3,4-butanetetrol (9a):

To a stirred solution of aldehyde (*R,R*)-**2** (0.3 g, 1.20 mmol) in CH_2Cl_2 (10 mL) was added at 0°C a solution of 2-(trimethylsilyl)thiazole[9] (0.19 g, 1.21 mmol) in the same solvent (5 mL). After stirring at r.t. for 16 h the solvent was evaporated under reduced pressure and the residue was dissolved in THF (15 mL) and treated with Bu_4NF 1 M solution in THF (1.2 mL, 1.20 mmol). After 1 h the solvent was partially evaporated under reduced pressure and the residue was treated with sat. aq $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was passed through a short column of silica gel (hexane/Et_2O, 60 : 40) to give 0.36 g (90%) of **9a** in 90% diastereomeric purity by NMR.

^{1}H NMR ($CDCl_3$ + D_2O) (selected): δ = 1.35 (s, 3H), 1.50 (s, 3H), 3.61 (dd, 1H, *J* = 10.3, 4.9 Hz), 3.84 (dd, 1H, *J* = 10.3, 5.1 Hz), 4.49 (m, 2H), 4.60 (br s, 2H), 5.10 (d, 1H, = 7.9 Hz), 7.32 (m, 6H), 7.78 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$ + D_2O) (selected): δ = 24.33, 26.81, 67.72, 69.41, 73.31, 75.34, 79.02, 108.34, 119.20, 127.64, 127.74, 128.21, 136.84, 141.72, 170.73.

Derivatization: The above crude product was treated with Ac_2O (1 mL) and pyridine (1 mL) in the presence of catalytic amount of DMAP for 12 h at r.t. The mixture was treated with sat. aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) filtered, and distilled under reduced pressure to give the crude product which was purified by flash chromatography on silica gel (hexane/Et_2O, 60 : 40) to afford pure **9b** as a colorless oil; yield: 0.35 g (85%); $[\alpha]_D^{20}$ −4.6° (*c* = 0.67, $CHCl_3$).

$C_{19}H_{23}NO_5S$	calc.	C 60.45	H 6.14	N 3.71
(377.5)	found	60.51	6.11	3.66

IR ($CHCl_3$): $\nu = 1735\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 3H), 1.38 (s, 3H), 1.92 (s, 3H), 3.49 (dd, 1H, *J* = 10.2, 7.1 Hz), 3.60 (dd, 1H, *J* = 10.2, 4.4 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.48 (m, 1H), 4.51 (d, 1H, *J* = 12.0 Hz), 4.66 (dd, 1H, *J* = 7.7, 6.1 Hz), 6.05 (d, 1H, *J* = 7.7 Hz), 7.39 (m, 6H), 7.72 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 19.67, 24.20, 26.55, 67.41, 69.52, 72.98, 76.03, 76.51, 108.91, 119.52, 127.38, 127.64, 127.99, 137.41, 142.34, 165.83, 168.98.

(3*S*,4*R*)-5-Benzyloxy-3,4-*O*-isopropylidenedioxy-1-(2-thiazolyl)-1-pentene (10):

To a well-stirred suspension of [(2-thiazolyl)methyl]triphenylphosphonium chloride[12] (0.4 g, 1 mmol) in benzene (20 mL) at r.t. was added KOBu-*t* (0.11 g, 1 mmol). After 1 h, a solution of the aldehyde (*R,R*)-**2** (0.25 g, 1 mmol) in benzene (5 mL) was added dropwise and stirring was continued for 12 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give 0.34 g (94%) of the alkene (*E/Z*)-**10** (57 : 43 ratio by NMR). A solution of this mixture and a few crystals of I_2 in 1,2-dichloroethane (20 mL) was refluxed for 72 h. The resulting red solution was washed with sat. aq $Na_2S_2O_3$ (20 mL), dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure. The crude material was chromatographed on silica gel (hexane/Et_2O, 70 : 30) to give:

(*Z*)-**10**: (R_f 0.48) as a yellow oil; yield: 0.03 g (9%); $[\alpha]_D^{20}$ + 232.1° (*c* = 0.84, $CHCl_3$).

$C_{18}H_{21}NO_3S$	calc.	C 65.23	H 6.39	N 4.23
(331.4)	found	65.08	6.59	4.31

^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3H), 1.54 (s, 3H), 3.41 (dd, 1H, *J* = 10.3, 7.1 Hz), 3.49 (dd, 1H, *J* = 10.3, 3.5 Hz), 4.46 (br s, 2H), 4.71 (dt, 1H, *J* = 7.1, 3.5 Hz), 5.74 (m, 1H), 5.90 (dd, 1H, *J* = 11.7, 8.0 Hz), 6.57 (dd, 1H, *J* = 11.7, 1.4 Hz), 7.25 (m, 6H), 7.76 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 24.33, 26.87, 68.99, 72.56, 74.05; 76.88, 108.56, 119.04, 121.85, 127.02, 127.19, 127.84, 133.10, 137.95, 143.62, 163.24.

(*E*)-**10**: (R_f 0.30) as a white solid; yield: 0.27 g (82%); mp 54–55°C; $[\alpha]_D^{20}$ −16.9° (*c* = 1.10, $CHCl_3$).

$C_{18}H_{21}NO_3S$	calc.	C 65.23	H 6.39	N 4.23
(331.4)	found	65.27	6.23	4.48

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3H), 1.49 (s, 3H), 3.42 (dd, 1H, *J* = 9.6, 5.9 Hz), 3.47 (dd, 1H, *J* = 9.6, 4.3 Hz), 4.38 (m, 1H), 4.40 (d, 1H, *J* = 11.7 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.76 (dt, 1H, *J* = 6.5, 1.2 Hz), 6.50 (dd, 1H, *J* = 15.9, 6.4 Hz), 6.84 (dd, 1H, *J* = 15.9, 1.2 Hz), 7.20 (m, 6H), 7.70 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 24.33, 26.86, 68.50, 72.82, 76.13, 76.48, 108.74, 118.02, 124.86, 127.25, 127.38, 127.93, 131.06, 137.53, 143.12, 165.77.

(3*R*,4*R*,5*R*)-3-Benzyl(*tert*-butoxycarbonyl)amino-6-benzyloxy-4,5-isopropylidenedioxyhexanal (11):

A solution of the (*E*)-**10** (0.25 g, 0.76 mmol) in MeCN (15 mL) was treated with MeI (1.08 g, 7.6 mmol) and then refluxed for 16 h. The solvent was removed under vacuum to give the *N*-methylthiazolium salt (0.36 g, 100%) as a sticky oil. The product obtained was pure enough for elaboration.

^{1}H NMR (D_2O): δ = 1.30 (s, 3H), 1.41 (s, 3H), 3.45 (dd, 1H, *J* = 10.1, 4.8 Hz), 3.54 (dd, 1H, *J* = 10.1, 5.2 Hz), 3.80 (s, 3H), 4.36 (br s, 2H), 4.50 (m, 1H), 4.90 (m, 1H), 6.81 (m, 2H), 7.20 (m, 5H), 7.71 (d, 1H, *J* = 3.6 Hz), 7.83 (d, 1H, *J* = 3.6 Hz).

^{13}C NMR (D_2O): δ = 26.51, 28.80, 41.48, 70.15, 75.81, 78.81, 79.25, 113.22, 118.63, 124.89, 131.33, 131.44, 131.53, 139.97, 141.34, 147.24, 170.78.

To a stirred solution of the above thiazolium salt (0.42 g, 0.89 mmol) in anhydr. MeOH (10 mL) at −50°C, benzylamine (0.12 g, 1.16 mmol) was added. After stirring for 4 h, $NaBH_4$ (50 mg, 1.32 mmol) was added portionwise and the mixture was allowed to warm to 0°C. Acetone (0.2 mL) was added and the solvent was evaporated under reduced pressure. The residue was treated with sat.

aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and distilled in vacuo.

The residue was dissolved in dioxane (5 mL) and treated with di-*tert*-butyl dicarbonate (Boc_2O) (0.22 g, 1 mmol). After stirring for 12 h at r.t. the mixture was concentrated, treated with sat. aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and distilled under reduced pressure to give an oily residue.

This crude material was dissolved in 1 mL of MeCN and added to a solution of $HgCl_2$ (0.27 g, 1 mmol) in MeCN/H_2O (4 : 1, 6 mL). The mixture was stirred for 15 min, filtered through Celite and the solvent evaporated. The residue was treated with sat. aq KI (10 mL) and extracted with $CHCl_3$ (2 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and the solvent distilled under reduced pressure to give the crude aldehyde in 93% diastereomeric purity by ^1H NMR. Purification of this material by column chromatography on silica gel (hexane/Et_2O, 60 : 40) affords pure **11** as a colorless oil; yield: 0.31 g (72%); $[\alpha]_D^{20}$ + 8.4° (*c* = 0.86, $CHCl_3$).

$C_{28}H_{37}NO_6$	calc.	C 69.54	H 7.71	N 2.90
(483.6)	found	69.33	7.75	2.92

IR ($CHCl_3$): ν = 1720 (b) cm^{-1}.

^1H NMR ($CDCl_3$, (80 MHz, 340 K): δ = 1.3 (s, 9 H), 1.54 (s, 3 H), 1.60 (s, 3 H), 2.48 (m, H), 3.34 (dd, 1 H, *J* = 9.8, 5.4 Hz), 3.51 (dd, 1 H, *J* = 9.8, 6.1 Hz), 4.12 (m, 1 H), 4.40 (m, 2 H), 4.51 (m, 4 H), 7.30, (m, 10 H), 9.42 (br s, 1 H).

Methyl 6-*O*-Benzyl-3-benzylamino-2,3-dideoxy-α-D-arabinopyranoside (+)-(12):

The aldehyde **11** (0.3 g, 0.62 mmol) was treated with a 8% HCl solution in anhydr. MeOH (10 mL). After stirring for 12 h at r.t. the solvent was distilled under reduced pressure and the residue was partitioned between sat. aq $NaHCO_3$ (20 mL) and EtOAc (25 mL). The organic layer was dried (Na_2SO_4), filtered and distilled under reduced pressure. The crude product was chromatographed on silica gel (Et_2O/EtOAc, 80 : 20) to give pure (+)-**12** as a sticky oil; yield: 0.20 g (90%); $[\alpha]_D^{20}$ + 27.3° (*c* = 0.15, $CHCl_3$).

$C_{21}H_{27}NO_4$	calc.	C 70.56	H 7.61	N 3.92
(357.5)	found	70.41	7.31	4.25

^1H NMR ($CDCl_3$ + D_2O): δ = 1.51 (ddd, 1 H, *J* = 13.0, 11.9, 3.6 Hz), 2.25 (ddd, 1 H, *J* = 13.0, 4.4, 1.2 Hz), 3.00 (ddd, 1 H, *J* = 11.9, 9.6, 4.5 Hz), 3.36 (s, 3 H), 3.42 (t, 1 H, *J* = 9.5 Hz), 3.70 (d, 1 H, *J* = 12.9 Hz), 3.75 (m, 2 H), 3.90 (d, 1 H, *J* = 12.9 Hz), 4.56 (m, 1 H), 4.60 (d, 1 H, *J* = 12.1 Hz), 4.64 (d, 1 H, *J* = 12.1 Hz), 4.84 (dd, 1 H, *J* = 3.6, 1.2 Hz), 7.34 (m, 10 H).

^{13}C NMR ($CDCl_3$ + D_2O): δ = 34.91, 50.48, 54.53, 55.56, 70.62, 70.73, 71.51, 73.55, 98.61, 127,37, 127.95, 128.03, 128.38, 128.49, 128.70, 138.50, 140.65.

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