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Characteristic alkaline catalyzed degradation of kotalanol, a potent α-glucosidase inhibitor isolated from Ayurvedic traditional medicine *Salacia reticulata*, leading to anhydroheptitols: another structural proof

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ABSTRACT

Stereochemical structure of kotalanol (**2**), a highly potent α-glucosidase inhibitor isolated from an Ayurvedic traditional medicine *Salacia reticulata*, was proved by alkaline catalyzed degradation of natural kotalanol (**2**), in which characteristic stereospecific cyclization of the degradative side chain leading to anhydroheptitols (**10** and **11**) was involved.

1. Introduction

Over the years, inhibitors of carbohydrate-processing enzymes viz. glycosidase inhibitors have received considerable attention in the field of chemical and medicinal research. They have many potential therapeutic applications because the glycosidase enzyme-catalyzed hydrolysis of complex carbohydrates is a widespread phenomenon in living systems.[1] From roots and stems of a *Salacia* species, which have traditionally been used for treatment of diabetes in Sri Lanka and India, the authors had isolated highly potent α-glucosidase inhibitors, salacinol (**1**) and kotalanol (**2**).[2] Their α-glucosidase inhibitory activities were revealed to be as high as those of voglibose and acarbose, which are widely used clinically these days.[2] Besides, their structures are quite unique, bearing thiosugar sulfonium sulfate inner salt comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 1-deoxy-aldosyl-3-sulfate anion as shown in Figure 1. Thereafter, their analogs, ponkolanol (**3**) and salaprinol (**4**),[3a] as well as *O*-desulfonated analogs (neosalacinol **5** and neokotalanol **6**)[4] were also isolated from several species of the same genus (Fig. 1).

Because of their intriguing structure and high α-glucosidase inhibitory activities, intensive structure–activity relationship (SAR) studies have been reported,[1,3,5] and through these studies, absolute stereochemistry of **1**,[2a,c] **3**,[3b] and **4**[6] was determined. While, stereochemical structure of **2** has long been left unclarified, although **2** and **6** are reported to be the most active principals in aqueous extracts of *Salacia reticulata*.[2b,3a] Most recently, through the intensive SAR studies directed toward the structural elucidation of **2**, Pinto and co-workers have accomplished the first total synthesis of **2** by an elegant manner, proving its exact stereostructure.[7] The

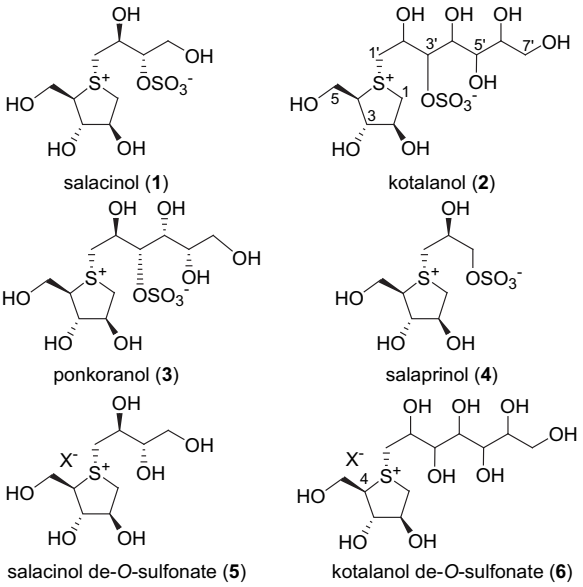

Figure 1.

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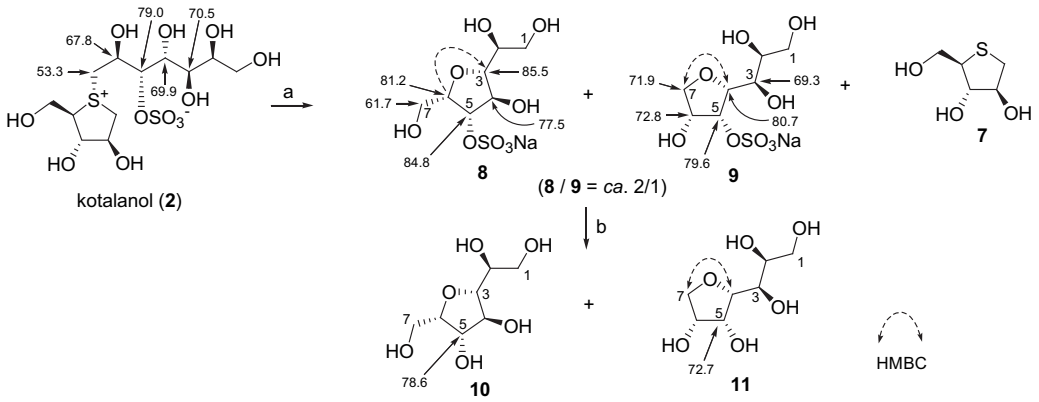
authors have also proved the stereostructure of **2** independently by an alkaline catalyzed degradation of natural kotalanol **2**, in which characteristic cyclization of the degraded side chain into anhydroheptitols was observed. In this paper full details of the process and the alternative synthesis of the degradative products are described.

1.1. Alkaline degradation of kotalanol (2)

Kotalanol (**2**) was treated with sodium methoxide in methanol at 50 °C for 3 h. Concomitant with the corresponding thiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol (**7**), a mixture of sodium salts of two anhydroheptitol sulfonates, sodium 3,6-anhydro-D-*glycero*-D-*galacto*-heptitol 5-*O*-sulfonate (**8**) and sodium 4,7-anhydro-D-*glycero*-D-*galacto*-heptitol 5-*O*-sulfonate (**9**), with a ratio of ca. 2:1, was obtained as a hardly separable mixture in 95% yield. These sulfonates **8** and **9** were characterized as shown in Scheme 1 on the basis of intensive 2D NMR spectroscopic studies. Observed highly deshielded signals (δ_{C3} 85.5 and δ_{C6} 81.2 for **8**, δ_{C4} 80.7 & δ_{C7} 71.9 for **9**) indicated the tetrahydrofuran ring formation, which was also supported by HMBC correlations observed between α-carbons in the tetrahydrofuran ring and appropriate protons as shown in Scheme 1. Another deshielded signals (δ_{C5} 84.8 for **8**, δ_{C5} 79.6 for **9**) suggested the presence of the sulfonyloxy moiety in the products. The mass spectrum of the mixture run in a negative mode gave a peak at *m*/*z* 273 corresponding to the sulfonate anion $[M-Na]^-$. The mixture was then subjected to an acid catalyzed methanolysis to afford corresponding anhydroheptitols, 3,6-anhydro-D-*glycero*-D-*galacto*-heptitol (**10**) and 4,7-anhydro-D-*glycero*-D-*galacto*-heptitol (**11**), in good yield. ^{1}H and ^{13}C NMR spectra of **8**, **9**, **10**, and **11** were summarized in Table 1. The physical and spectral properties of **11** were completely in accord with those of the authentic specimen obtained via an alternative route as described in the next Section 1.2.

The formation of the major sulfonate **8** would be ascribed, as shown in Scheme 2, to the nucleophilic attack of an alkoxide anion at C-3 (intermediate A) to the epoxide moiety formed as an intermediate under the basic conditions (route a), while the minor one **9** would be formed through the direct attack of an alkoxide ion at C-4′ to C1′ methylene carbon of the side chain (route b).

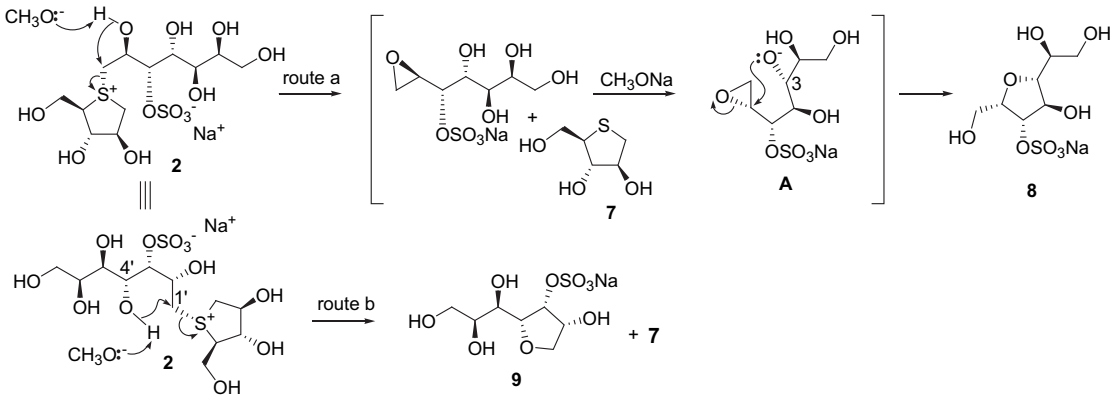


Scheme 1. Reagents and conditions: (a) $NaOCH_3$, MeOH, 50 °C; (b) 5% methanolic HCl, 50 °C.

Table 1
^{1}H and ^{13}C NMR data for compounds **8** and **9** (500 MHz), **10** and **11** (700 MHz) in CD_3OD

	δ_H	δ_C	δ_H	δ_C
	Compound **8**		Compound **9**	
H-1a	3.59 (dd, *J*=11.2, 6.3)	64.6	3.63–3.68 (2H, m)	64.6
H-1b	3.66 (dd, *J*=11.2, 5.5)			
H-2	3.72 (ddd, *J*=6.3, 5.5, 5.5)	72.9	3.80 (ddd, *J*=7.0, 6.0, 1.4)	71.7
H-3	3.68 (dd, *J*=5.5, 5.5)	85.5	3.95 (dd, *J*=9.5, 1.4)	69.3
H-4	4.36 (dd, *J*=5.5, 3.5)	77.5	4.10 (dd, *J*=9.5, 3.5)	80.7
H-5	4.70 (dd, *J*=5.2, 3.5)	84.8	4.88 (dd, *J*=4.6, 3.5)	79.6
H-6	4.15 (ddd, *J*=6.3, 5.2, 4.6)	81.2	4.49 (ddd, *J*=8.6, 7.7, 4.6)	72.8
H-7a	3.73 (dd, *J*=12.0, 6.3)	61.7	3.60 (dd, *J*=8.6, 8.6)	71.9
H-7b	3.82 (dd, *J*=12.0, 4.6)		3.82 (dd, *J*=8.6, 7.7)	
	Compound **10**		Compound **11**	
H-1a	3.60 (dd, *J*=11.2, 6.4)	64.5	3.61 (dd, *J*=11.1, 6.9)	64.6
H-1b	3.64 (dd, *J*=11.2, 5.6)		3.636 (dd, *J*=11.1, 6.0)	
H-2	3.74 (ddd, *J*=6.4, 5.6, 3.0)	72.9	3.77 (ddd, *J*=6.9, 6.0, 1.8)	72.3
H-3	3.79 (dd, *J*=3.8, 3.0)	86.1	3.92 (dd, *J*=8.8, 1.8)	70.1
H-4	4.09 (dd, *J*=3.8, 2.6)	80.2	3.89 (dd, *J*=8.8, 3.5)	81.4
H-5	3.99 (dd, *J*=4.4, 2.6)	78.6	4.19 (dd, *J*=4.6, 3.5)	72.7
H-6	4.02 (ddd, *J*=6.0, 4.4, 4.4)	82.6	4.33 (ddd, *J*=7.0, 7.0, 4.6)	73.2
H-7a	3.72 (dd, *J*=11.6, 6.0)	61.8	3.640 (dd, *J*=8.5, 7.0)	72.1
H-7b	3.78 (dd, *J*=11.6, 4.4)		3.87 (dd, *J*=8.5, 7.0)	

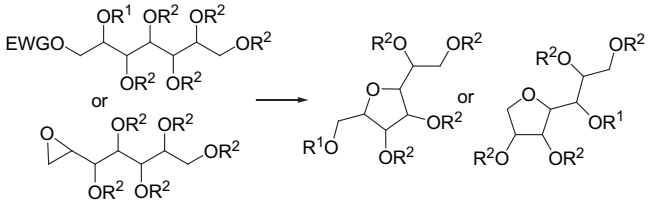
^{1}H chemical shift values (δ ppm) are followed by the multiplicity of the signal and the coupling constants (J/Hz).



Scheme 2. Plausible mechanism for the formation of compounds **8** and **9**.

1.2. Alternative synthesis of the degradation product (11)

In the course of synthetic studies[8] on kotalanol (**2**), the authors have encountered characteristic deprotective cyclo-etherification of polyprotected heptitols to anhydroheptitols as shown in Scheme 3. One of the anhydroheptitols thus derived from a heptitol derivative, 1,2;3,4;5,6-tri-*O*-isopropyridene-D-*glycero*-D-*galacto*-heptitol 7-*O*-trifrate (**12**), was in accord with the degradative product (**11**), which led to the unambiguous identification of the product (**11**).



EWG: electron withdrowing group
R = H, alkyl *etc*.

Scheme 3. Charateristic deprotective cyclo-etherification of heptitols.

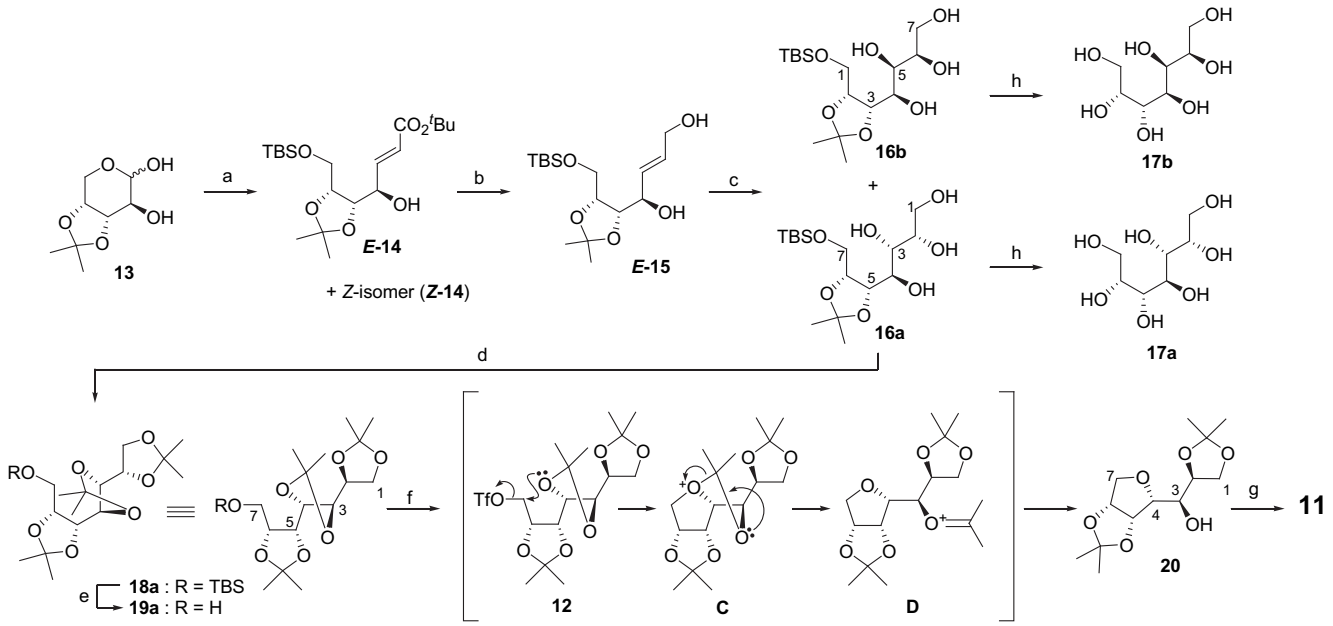
Thus, compound **11** was prepared as following. According to the literature,[9] D-arabinose was converted to 3,4-*O*-isopropylidene-D-arabinopyranose (**13**). The Wittig reaction of **13** with *tert*-butoxycarbonylmethylenetriphenylphosphorane followed by treatment of the resulting mixture with TBSCl afforded a mixture of corresponding olefinic esters, *tert*-butyl (*E*)-7-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-5,6-*O*-isopropylidene-D-*arabino*-hept-2-enoate (*E*-**14**) and its *Z*-isomer (*Z*-**14**) in 41% and 35% yield, respectively. After the ester moiety of *E*-**14** was reduced with DIBAL, the resulting allyl alcohol, (*E*)-7-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-5,6-*O*-isopropylidene-D-*arabino*-hept-2-enitol (***E*-15**) was subjected to dihydroxylation by osmium tetroxide to give a mixture of 7-*tert*-butyldimethylsilyl-5,6-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**16a**) and 1-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-*glycero*-L-*gulo*-heptitol (**16b**) in 38% and 13% yield, respectively. The structure of the major isomer **16a** was confirmed by comparison of its ^{13}C NMR spectroscopic properties with those of D-*glycero*-D-*galacto*-heptitol[10] (**17a**) after deprotection of all the protective groups of **16a** by treatment with 1% hydrochloric acid. Acid catalyzed hydrolysis of the minor one (**16b**) also gave the corresponding heptitol, D-*glycero*-L-*gulo*-heptitol (**17b**), whose ^{13}C NMR spectroscopic properties were in accordance with those reported.[10a] From the major isomer (**16a**) was obtained trisacetonide, 7-*O*-*tert*-butyldimethylsilyl-1,2;3,4;5,6-tri-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**18a**) by treatment with excess $(CH_3)_2C(OCH_3)_2$ in 42% yield. Selective deprotection of the TBS group in **18a** was accomplished by using TBAF to give 1,2;3,4;5,6-tri-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**19a**) in 94% yield. Attempted sulfonation of **19a** with trifluoromethanesulfonic anhydride caused cyclization of the resultant triflate (**12**) to afford 4,7-anhydro-1,2;5,6-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**20**) in 77% yield. The formation of the tetrahydrofuran derivative **20** would be attributed to stereospecific deprotective cyclo-etherification[11] of **12** as shown in Scheme 4. Acid catalyzed deprotection of tetrahydrofuran derivative **20** with 5% methanolic hydrogen chloride gave anhydroheptitol (**11**), the spectroscopic properties of which were completely in accordance with those of the degradation product (**11**).

Thus, the side chain of kotalanol (**2**) was elucidated to be 7-deoxy-D-*glycero*-D-*galacto*-heptitol, a heptitol of 2′*S*,3′*S*,4′*R*,5′*R*,6′*S* stereochemistry, and the exact stereochemistry of the side chain of **2** has been successfully proved. The present work has provided the proof of the stereostructure of **2** in an independent manner, and the results of these two works were totally consistent. In a previous report by one of the authors[2b] was a transcription error with respect to the δ value of the H5′ proton as was indicated by Pinto and co-workers.[7] In the present study the error has been corrected (δ_H 5.86[2b]→4.86), and the ^1H and ^{13}C NMR spectroscopic data of natural kotalanol (**2**) in D_2O and in CD_3OD are also presented in Table 2. Discrepancy on the specific rotation of **2** with the literature[7] has also been reexamined. Repeated measurements of optical rotation of **2** in MeOH in the present study gave inconsistent results, among which the value corresponding to the one we had reported {$[\alpha]_D^{27}$ +11.5 (MeOH)}[2b] was involved. After careful refiltration of the solution, we could obtain consistent and reproducible value of $[\alpha]_D^{24}$ −6.9 (*c* 0.34, CH_3OH), which was in good accordance with the Pinto's report {$[\alpha]_D^{23}$ −5.7 (*c* 0.7, MeOH)}.[7] Thus, we attribute the discrepancy to our insufficient filtration of the solution, and to invisible particles, which might be caused by either the poor solubility of kotalanol in MeOH or other concomitants introduced during the isolation. Aqueous solution of **2** gave reproducible specific rotation {$[\alpha]_D^{24}$ +6.7 (*c* 0.30, H_2O)}, which was in agreement with the one {$[\alpha]_D^{24}$ +7.0 (*c* 0.6, H_2O)} reported.[7]

2. Experimental

2.1. General

Mps were determined on a Yanagimoto MP-3S micromelting point apparatus, and mps and bps are uncorrected. IR spectra were measured on either a Shimadzu IR-435 grating spectrophotometer or a Shimadzu FTIR-8600PC spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz ^1H, 125 MHz ^{13}C) or a JEOL JNM-ECA 700 (700 MHz ^1H, 175 MHz ^{13}C) spectrometer. Chemical shifts (δ) and coupling constants (*J*) are given in parts per



Scheme 4. Reagents and conditions: (a) $Ph_3P{=}CHCO_2{}^tBu$, CH_3CN, 60 °C, then TBSCl, imidazole, 0 °C; (b) DIBAL, toluene–THF, −15 °C to rt; (c) OsO_4, NMO, acetone–H_2O, reflux; (d) $(CH_3)_2C(OCH_3)_2$, TsOH, acetone, 0 °C; (e) TBAF, THF–H_2O, 70 °C; (f) Tf_2O, 2,6-lutidine, CH_2Cl_2, −15 °C to 0 °C; (g) 5% methanolic HCl, 60 °C; (h) 1% aq HCl, MeOH, reflux.

Table 2
^1H (600 MHz) and ^{13}C (150 MHz) NMR data for kotalanol (**2**) in CD_3OD and in D_2O

	In CD_3OD		In D_2O	
	δ_H	δ_C	δ_H	δ_C
H-1a	3.81 (d-like, *J*=2.8)	51.1	3.75 (d-like, *J*=3.4)	47.8
H-1b				
H-2	4.60 (td, *J*=2.8, 2.8)	79.0	4.61 (td, *J*=3.4, 3.4)	76.8
H-3	4.43 (br d-like)	79.9	4.33 (dd-like, *J*=3.4, 3.4)	77.8
H-4	4.00 (m)	73.0	3.96 (ddd-like, *J*=7.6, 5.5, 3.4)	70.0
H-5a	3.97 (m)	60.8	3.83 (dd, *J*=11.0, 7.6)	59.1
H-5b	4.03 (m)		3.98 (dd, *J*=11.0, 5.5)	
H-1′a	3.99 (dd, *J*=13.4, 8.5)	53.3	3.78 (dd, *J*=13.8, 7.6)	50.8
H-1′b	4.08 (dd, *J*=13.4, 3.8)		3.97 (dd, *J*=13.8, 3.4)	
H-2′	4.44 (m)	67.8	4.32 (ddd, *J*=8.2, 7.6, 3.4)	66.2
H-3′	4.62 (dd, *J*=8.6, 1.0)	79.0	4.53 (d-like, *J*=8.2)	78.4
H-4′	4.04 (d-like, *J*=10.3)	69.9	3.86 (d-like, *J*=10.3)	68.0
H-5′	3.78 (dd, *J*=9.6, 1.4)	70.5	3.66 (dd, *J*=10.3, 1.4)	68.7
H-6′	3.95 (m)	71.8	3.85 (ddd-like, *J*=7.6, 5.5, 1.4)	70.0
H-7′a	3.66 (dd, *J*=11.2, 7.1)	65.1	3.54 (dd, *J*=11.6, 7.6)	63.3
H-7′b	3.69 (dd, *J*=11.2, 6.0)		3.56 (dd, *J*=11.6, 5.5)	

^1H chemical shift values (δ ppm) are followed by the multiplicity of the signal and the coupling constants (*J*/Hz).

million and hertz, respectively. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCO P-2200 polarimeter. Column chromatography was effected over Fuji Silysia Chemical silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

2.2. Alkaline degradation of kotalanol (2)

A mixture of kotalanol (**2**, 5.8 mg, 0.014 mmol), sodium methoxide (36 mg, 0.67 mmol), and methanol (1.8 ml) was heated at 50 °C for 3 h. After being cooled, the reaction mixture was neutralized with amberlite IR-120 PLUS (H^+ form) and condensed to give a colorless oil, which on column chromatography ($CHCl_3$–MeOH, 5:1) gave thiosugar[5b] **7** (2.0 mg, 98%) and a hardly separable ca. 2:1 mixture (3.8 mg, 95%) of sodium salts of two anhydroheptitol sulfonates, sodium 3,6-anhydro-D-*glycero*-D-*galacto*-heptitol 5-*O*-sulfonate (**8**) and sodium 4,7-anhydro-D-*glycero*-D-*galacto*-heptitol 5-*O*-sulfonate (**9**). FABMS *m*/*z*: (neg.) 273 $[M-Na]^-$. ^1H and ^{13}C data for **8** and **9** extracted from NMR spectra of the mixture were summarized in Table 1.

2.3. Acid catalyzed methanolysis of degradation products 8 and 9

A mixture of two anhydroheptitol 5-*O*-sulfonates (**8** and **9**, 3.8 mg) was treated with 5% methanolic hydrogen chloride (0.6 ml) at 50 °C for 1.5 h. Removal of the solvent left a colorless oil (4.1 mg), which on column chromatography ($CHCl_3$–MeOH, 5:1) gave a hardly separable ca. 2:1 mixture (2.4 mg, 95%) of 3,6-anhydro-D-*glycero*-D-*galacto*-heptitol (**10**) and 4,7-anhydro-D-*glycero*-D-*galacto*-heptitol (**11**). FABMS *m*/*z*: (pos.) 217 $[M+Na]^+$. ^1H and ^{13}C data for compounds **10** and **11** extracted from NMR spectra of the mixture were summarized in Table 1.

2.4. (*E*)-7-*O*-*tert*-Butyl dimethylsilyl-2,3-dideoxy-5,6-*O*-isopropylidene-D-*arabino*-hept-2-enoate (*E*-14) and its *Z*-isomer (*Z*-14)

A mixture of 3,4-*O*-isopropylidene-D-arabinopyranose[9] (**13**, 2.77 g, 14.6 mmol), *tert*-butoxycarbonylmethylenetriphenylphosphorane (8.23 g, 21.9 mmol), and acetonitrile (30 ml) was heated at 60 °C for 2 h. After removal of the solvent, the residue was

triturated with a mixture of *n*-hexane and diethyl ether (2:1). The solidified material was filtered and washed with a mixture of *n*-hexane and diethyl ether (2:1). The combined filtrate and washings were condensed to give a pale yellow oil (8.5 g), which was then silylated with *tert*-butyldimethylsilyl chloride (2.22 g, 14.7 mmol) in dimethylformamide (40 ml) in the presence of imidazole (1.9 g, 27.6 mmol) at 0 °C for 3 h. The reaction mixture was poured into water, and the resulting mixture was extracted with a mixture of *n*-hexane and diethyl ether (2:1). The extract was washed with brine, and condensed to give a pale yellow oil (5.4 g), which on column chromatography (*n*-hexane–acetone, 50:1) gave the title *E*-olefinic ester (*E*-**14**, 2.41 g, 41%) and its *Z*-isomer *Z*-**14** (2.05 g, 35%).

*2.4.1. Olefinic ester E-**14**.* Colorless oil. $[\alpha]_D^{23}$ +0.30 (*c* 1.2, $CHCl_3$). IR (neat): 3352, 1601, 1458, 1381, 1250, 1219, 1072, 1049 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.10 [6H, s, $^tBu(CH_3)_2Si$], 0.90 [9H, s, $(CH_3)_3CMe_2Si$], 1.36/1.49 [each 3H, s, $C(CH_3)_2$], 1.48 [9H, s, $CO_2C(CH_3)_3$], 3.27 (1H, d, *J*=6.3 Hz, C4–OH), 3.76 (1H, dd, *J*=10.9, 3.7 Hz, H-7a), 3.94 (1H, dd, *J*=10.9, 7.5 Hz, H-7b), 4.20 (1H, dd, *J*=6.3, 3.7 Hz, H-5), 4.23 (1H, ddd, *J*=7.5, 6.3, 3.7 Hz, H-6), 4.54 (1H, dddd, *J*=6.3, 4.0, 3.7, 2.0 Hz, H-4), 6.10 (1H, dd, *J*=15.8, 2.0 Hz, H-2), 6.95 (1H, dd, *J*=15.8, 4.0 Hz, H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.50 [$^tBu(CH_3)_2Si$], 18.2 [$(CH_3)_3CMe_2Si$], 24.8/27.0 [$C(CH_3)_2$], 25.8 [$(CH_3)_3CMe_2Si$], 28.1 [$CO_2C(CH_3)_3$], 61.5 (C-7), 68.8 (C-4), 77.0 (C-6), 78.8 (C-5), 80.3 [$CO_2C(CH_3)_3$], 108.5 [$C(CH_3)_2$], 123.5 (C-2), 145.6 (C-3), 165.7 [$CO_2C(CH_3)_3$]. FABMS *m*/*z*: (pos.) 425 $[M+Na]^+$.

*2.4.2. Olefinic ester Z-**14**.* Colorless oil. $[\alpha]_D^{24}$ +2.33 (*c* 0.90, $CDCl_3$). IR (neat): 3383, 1633, 1458, 1392, 1259, 1107, 1087, 1037 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ: 0.11 [6H, s, $^tBu(CH_3)_2Si$], 0.92 [9H, s, $(CH_3)_3CMe_2Si$], 1.36/1.53 [each 3H, s, $C(CH_3)_2$], 1.47 [9H, s, $CO_2C(CH_3)_3$], 3.88 (1H, dd, *J*=11.3, 3.7 Hz, H-7a), 4.01 (1H, d, *J*=4.9 Hz, C4–OH), 4.03 (1H, dd, *J*=11.3, 5.8 Hz, H-7b), 4.25 (1H, ddd, *J*=6.6, 5.8, 3.7 Hz, H-6), 4.27 (1H, dd, *J*=6.6, 2.3 Hz, H-5), 5.24 (1H, dddd, *J*=7.3, 4.9, 2.3, 1.5 Hz, H-4), 5.77 (1H, dd, *J*=11.8, 1.5 Hz, H-2), 6.28 (1H, dd, *J*=11.8, 7.3 Hz, H-3). ^{13}C NMR (150 MHz, $CDCl_3$) δ: −5.46/−5.43 [$^tBu(CH_3)_2Si$], 18.4 [$(CH_3)_3CMe_2Si$], 25.1/26.9 [$C(CH_3)_2$], 25.8 [$(CH_3)_3CMe_2Si$], 28.1 [$CO_2C(CH_3)_3$], 61.5 (C-7), 66.5 (C-4), 77.5 (C-6), 79.8 (C-5), 80.7 [$CO_2C(CH_3)_3$], 108.4 [$C(CH_3)_2$], 121.8 (C-2), 148.8 (C-3), 165.7 [$CO_2C(CH_3)_3$]. FABMS *m*/*z*: (pos.) 425 $[M+Na]^+$.

2.5. (*E*)-7-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-5,6-*O*-isopropylidene-D-*arabino*-hept-2-enitol (*E*-15)

To a solution of the olefinic ester *E*-**14** (1.5 g, 3.73 mmol) in tetrahydrofuran (50 ml) was added dropwise a 1 M solution of diisobutylaluminum hydride in toluene (18 ml, 18 mmol) at −15 °C. After being stirred at −15 °C for 1 h, the reaction mixture was allowed to reach room temperature, and was stirred for 2 h. The reaction was quenched with water (10 ml), and the resulting mixture was diluted with ethyl acetate (50 ml). The deposited gel was filtered through Celite and washed with ethyl acetate. The combined filtrate and washings were condensed to give the title olefinic alcohol (*E*-**15**, 1.24 g) as a colorless oil, which was used in the next step without purification. Analytical sample of the olefinic alcohol *E*-**15** was obtained by means of column chromatography (*n*-hexane–acetone, 20:1→10:1) of a small portion of the crude product.

*2.5.1. Olefinic alcohol E-**15**.* $[\alpha]_D^{23}$ −8.84 (*c* 0.43, $CDCl_3$). IR (neat): 3425, 1594, 1465, 1366, 1250, 1215, 1078 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.10 [6H, s, $^tBu(CH_3)_2Si$], 0.91 [9H, s, $(CH_3)_3CMe_2Si$], 1.69 (1H, br s, OH), 1.37/1.49 [each 3H, s, $C(CH_3)_2$], 3.12 (1H, d, *J*=5.5 Hz, C4–OH), 3.77 (1H, dd, *J*=10.9, 4.3 Hz, H-7a), 3.95 (1H, dd, *J*=10.9, 6.9 Hz, H-7b), 4.11 (1H, dd, *J*=6.6, 4.0 Hz, H-5), 4.16–4.20 (2H, m, H-1a and H-1b), 4.20 (1H, ddd, *J*=6.9, 6.6, 4.3 Hz, H-6), 4.39 (1H, dddd, *J*=5.5, 5.5, 4.0, 1.2 Hz, H-4), 5.88 (1H, ddt, *J*=15.7, 5.5, 2.9 Hz, H-3), 5.99 (1H, dtd, *J*=15.7, 5.2, 1.2 Hz, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.45 [$^tBu(CH_3)_2Si$], 18.3 [$(CH_3)_3CMe_2Si$], 24.9/27.1 [$C(CH_3)_2$], 25.8 [$(CH_3)_3CMe_2Si$], 61.7 (C-7), 63.1 (C-1), 69.3 (C-4), 77.3 (C-6), 79.7 (C-5), 108.3 [$C(CH_3)_2$],130.8 (C-3), 130.9 (C-2).

2.6. Dihydroxylation of olefinic alcohol *E*-15

A mixture of crude olefinic alcohol *E*-**15** (1.24 g), 0.039 M aqueous osmium tetroxide (4.8 ml, 0.19 mmol), *N*-methylmorphorine *N*-oxide (874 mg, 7.46 mmol), and acetone (30 ml) was heated under reflux for 4 h. After the reaction was quenched by the addition of sodium sulfite (940 mg, 7.46 mmol), the resulting mixture was condensed at reduced pressure. The residue was diluted with water (10 ml) and extracted with ethyl acetate. The extract was condensed to give a pale brown oil (1.73 g), which on column chromatography ($CHCl_3$→$CHCl_3$–MeOH, 50:1) gave 7-*tert*-butyldimethylsilyl-5,6-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**16a**, 520 mg, 38% from *E*-**14**) and 1-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-*glycero*-L-*gulo*-heptitol (**16b**, 180 mg, 13% from *E*-**14**).

*2.6.1. Compound **16a**.* Waxy solid. Mp 80–81 °C. $[\alpha]_D^{23}$ +6.29 (*c* 0.97, CH_3OH). IR (KBr): 3391, 1437, 1384, 1254, 1223, 1111, 1084, 1034 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 0.11 [6H, s, $^tBu(CH_3)_2Si$], 0.92 [9H, s, $(CH_3)_3CMe_2Si$], 1.35/1.46 [each 3H, s, $C(CH_3)_2$], 3.55 (1H, dd, *J*=9.2, 1.4 Hz, H-3), 3.62 (2H, d, *J*=6.3 Hz, H-1a and H-1b), 3.75 (1H, dd, *J*=9.2, 2.0 Hz, H-4), 3.88 (1H, dd, *J*=10.9, 6.0 Hz, H-7a), 3.93 (1H, td, *J*=6.3, 1.4 Hz, H-2), 3.95 (1H, dd, *J*=10.9, 4.6 Hz, H-7b), 4.27 (1H, ddd, *J*=7.2, 6.0, 4.6 Hz, H-6), 4.49 (1H, dd, *J*=7.2, 2.0 Hz, H-5). ^{13}C NMR (125 MHz, CD_3OD) δ: −5.18 [$^tBu(CH_3)_2Si$], 19.3 [$(CH_3)_3CMe_2Si$], 25.2/27.3 [$C(CH_3)_2$], 26.4 [$(CH_3)_3CMe_2Si$], 64.1 (C-7), 65.0 (C-1), 69.6 (C-4), 71.4 (C-2), 72.1 (C-3), 77.1 (C-5), 79.4 (C-6), 109.0 [$C(CH_3)_2$]. FABMS *m*/*z*: (pos.) 389 $[M+Na]^+$.

*2.6.2. Compound **16b**.* Waxy solid. Mp 69–70 °C. $[\alpha]_D^{23}$ −5.94 (*c* 0.96, CH_3OH). IR (KBr): 3417, 1469, 1384, 1258, 1219, 1150, 1084, 1049 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 0.10 [6H, s, $^tBu(CH_3)_2Si$], 0.92 [9H, s, $(CH_3)_3CMe_2Si$], 1.34/1.46 [each 3H, s, $C(CH_3)_2$], 3.61 (1H, dd, *J*=11.2, 6.3 Hz, H-7a), 3.65 (1H, dd, *J*=11.2, 4.9 Hz, H-7b), 3.68 (1H, dd, *J*=4.3, 4.0 Hz, H-5), 3.78 (1H, ddd, *J*=6.3, 4.9, 4.0 Hz, H-6), 3.80 (1H, dd, *J*=11.2, 5.7 Hz, H-1a), 3.89 (1H, dd, *J*=4.3, 4.3 Hz, H-4), 3.91 (1H, dd, *J*=11.2, 5.2 Hz, H-1b), 4.21 (1H, dd, *J*=6.6, 5.7, 5.2 Hz, H-2), 4.38 (1H, dd, *J*=6.6, 4.3 Hz, H-3). ^{13}C NMR (125 MHz, CD_3OD) δ: −5.21/−5.16 [$^tBu(CH_3)_2Si$], 19.3 [$(CH_3)_3CMe_2Si$], 25.4/27.6 ($C(CH_3)_2$), 26.5 [$(CH_3)_3CMe_2Si$], 63.8 (C-1), 64.5 (C-7), 71.0 (C-4), 73.0 (C-5), 73.8 (C-6), 78.3 (C-3), 79.2 (C-2), 109.5 ($C(CH_3)_2$). FABMS *m*/*z*: (pos.) 389 $[M+Na]^+$.

2.7. Confirmation of stereochemistry of tetrols 16a and 16b

A mixture of tetrol **16a** (10 mg, 0.027 mol), 1% hydrochloric acid (0.2 ml), and methanol (0.6 ml) was heated under reflux for 1.5 h. Condensation of the mixture left a colorless solid (5.8 mg), whose ^{13}C NMR spectroscopic properties were in good accordance with those of D-*glycero*-D-*galacto*-heptitol (**17a**) reported.[10a]

Following the method used for the deprotection of **16a**, tetrol **16b** (10 mg, 0.027 mol) was treated with 1% hydrochloric acid. Work-up in a manner similar to that used for the preparation of **17a** gave a colorless oil (5.8 mg), whose ^{13}C NMR spectroscopic properties were in good accordance with those of D-*glycero*-L-*gulo*-heptitol (**17b**) reported.[10a]

2.8. 7-*O*-*tert*-Butyldimethylsilyl-1,2;3,4;5,6-tri-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (18a)

A mixture of tetrol **16a** (180 mg, 0.49 mmol), 2,2-dimethoxypropane (2 ml, 16 mmol), *p*-tosic acid (40 mg), and acetone (2 ml) was stirred at 0 °C for 2 h. After the reaction was quenched by the

addition of aqueous sodium hydrogen carbonate (40 ml), the resulting mixture was extracted with dichloromethane. The extract was washed with brine, and condensed to give a pale yellow oil (220 mg), which on column chromatography (*n*-hexane–acetone, 80:1→50:1→20:1) gave the title compound (**18a**, 92 mg, 42%).

*2.8.1. Compound **18a**.* Colorless oil. $[\alpha]_D^{26}$ +31.3 (*c* 0.8, $CHCl_3$). IR (neat): 1462, 1373, 1250, 1219, 1157, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.067/0.074 [each 3H, s, ^{t}Bu(CH_3)$_2$Si], 0.89 [9H, s, (CH_3)$_3$CMe$_2$Si], 1.380(3H)/1.384(6H)/1.45(3H)/1.46(3H)/1.56(3H) [each s, C(CH_3)$_2$], 3.59 (1H, dd, *J*=9.5, 4.0 Hz, H-7a), 3.78 (1H, dd, *J*=9.5, 9.5 Hz, H-7b), 3.81 (1H, dd, *J*=7.7, 7.7 Hz, H-1a), 4.01 (1H, dd, *J*=7.7, 6.3 Hz, H-1b), 4.18 (1H, ddd, *J*=9.5, 5.5, 4.0 Hz, H-6), 4.20 (1H, m, H-3), 4.22 (1H, ddd, *J*=7.7, 6.3, 3.8, Hz, H-2), 4.43 (1H, dd, *J*=7.2, 7.2 Hz, H-4), 4.45 (1H, dd, *J*=7.2, 5.5 Hz, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.55/−5.36 [^{t}Bu(CH_3)$_2$Si], 18.4 [(CH_3)$_3$CMe$_2$Si], 25.08/25.59/25.85/26.41/26.84/27.78 [C(CH_3)$_2$], 25.9 [(CH_3)$_3$CMe$_2$Si], 62.1 (C-7), 66.4 (C-1), 75.2 (C-2), 75.3 (C-4), 75.7 (C-5) 76.4 (C-3), 76.8 (C-6), 108.5/109.1/109.7 [C(CH$_3$)$_2$]. FABMS *m*/*z*: (pos.) 469 $[M+Na]^+$.

2.9. 1,2;3,4;5,6-Tri-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (19a)

A mixture of compound **18a** (70 mg, 0.16 mmol), a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.7 ml, 0.7 mmol), tetrahydrofuran (2 ml), and water (0.2 ml) was heated at 70 °C for 2 h. After being cooled, the mixture was poured into ice-water (20 ml) and extracted with ethyl acetate. The extract was washed with brine and condensed to give a pale yellow oil (67 mg), which on column chromatography (*n*-hexane–ethyl acetate, 10:1) gave the title compound (**19a**, 49 mg, 94%).

*2.9.1. Compound **19a**.* Colorless oil. $[\alpha]_D^{25}$ +30.6 (*c* 0.8, $CHCl_3$). IR (neat): 3479, 1456, 1373, 1248, 1216, 1061, 1047 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 1.384/1.385/1.40/1.47/1.52/1.58 [each 3H, s, C(CH_3)$_2$], 2.50 (1H, br s, OH), 3.67 (1H, dd, *J*=11.8, 5.0 Hz, H-7a), 3.71 (1H, dd, *J*=11.8, 5.6 Hz, H-7b), 3.75 (1H, dd, *J*=8.0, 6.6 Hz, H-1a), 4.09 (1H, dd, *J*=8.0, 6.6 Hz, H-1b), 4.16 (1H, dd, *J*=6.2, 4.0 Hz, H-5), 4.218 (1H, ddd, *J*=6.2, 5.6, 5.0 Hz, H-6), 4.223 (1H, dd, *J*=6.6, 6.6 Hz, H-3), 4.35 (1H, dd, *J*=6.6, 4.0 Hz, H-4), 4.36 (1H, ddd, *J*=6.6, 6.6, 6.6 Hz, H-2). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 25.33/25.34/25.53/26.58/26.61/27.4 [C(CH_3)$_2$], 61.8 (C-7), 66.2 (C-1), 74.2 (C-4), 75.00 (C-2), 75.02 (C-5), 77.6 (C-6), 78.2 (C-3), 109.0/109.8/110.0 [C(CH$_3$)$_2$]. FABMS *m*/*z*: (pos.) 355 $[M+Na]^+$.

2.10. 4,7-Anhydro-1,2;5,6-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (20)

A solution of compound **19a** (20 mg, 0.06 mmol) was added to a mixture of trifluoromethanesulfonic anhydride (100 μl, 0.6 μmol), lutidine (0.35 ml, 3 mmol), and dichloromethane (1 ml) at −15 °C, and the reaction mixture was stirred at 0 °C for 5 h. After addition of aqueous sodium hydrogen carbonate (5 ml), the resulting mixture was extracted with ethyl acetate. The extract was washed with brine and condensed to give a brown oil (50 mg), which on column chromatography (chloroform) gave the title compound (**20**, 12.7 mg, 77%).

*2.10.1. Compound **20**.* Colorless oil, $[\alpha]_D^{26}$ −36.5 (*c* 0.6, $CHCl_3$). IR (neat): 3472, 1456, 1373, 1255, 1209, 1159, 1105, 1087, 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.35/1.39/1.46/1.49 [each 3H, s, C(CH_3)$_2$], 2.52 (1H, br s, OH), 3.42 (1H, dd, *J*=8.6, 4.0 Hz, H-4), 3.50 (1H, dd, *J*=10.9, 3.7 Hz, H-7a), 3.87 (1H, dd, *J*=8.6, 4.3 Hz, H-3), 3.96 (1H, dd, *J*=8.3, 6.9, Hz, H-1a), 4.02 (1H, d, *J*=10.9 Hz, H-7b), 4.07 (1H, dd, *J*=8.3, 6.9 Hz, H-1b), 4.31 (1H, ddd, *J*=6.9, 6.9, 4.3 Hz, H-2), 4.78 (1H, dd, *J*=6.0, 3.7 Hz, H-6), 4.82 (1H, dd, *J*=6.0, 4.0 Hz, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.6/25.2/26.0/26.4 [C(CH_3)$_2$], 66.1 (C-1), 69.1 (C-3), 73.2 (C-7), 76.5 (C-2), 80.6 (C-6) 80.7 (C-5), 82.4 (C-4), 109.2/112.2 [C(CH$_3$)$_2$]. FABMS *m*/*z*: (pos.) 275 $[M+H]^+$.

2.11. 4,7-Anhydro-D-*glycero*-D-*galacto*-heptitol (11)

A solution of the bisacetonide **20** (6.2 mg, 0.02 mmol) in 5% methanolic hydrogen chloride (0.8 ml) was stirred at 60 °C for 24 h. Concentration of the mixture left the title compound **11** (4.4 mg) as a pale yellow solid. Analytical sample was obtained by recrystallization from a mixture of diethyl ether and methanol.

*2.11.1. Compound **11**.* Colorless prisms. Mp 129–129.5 °C. $[\alpha]_D^{26}$ −12.8 (*c* 0.46, CH_3OH). IR (KBr): 3389, 1419, 1397, 1383, 1329, 1287, 1252, 1228, 1206, 1188, 1148, 1111, 1099, 1078, 1057, 1040 cm^{-1}. FABMS *m*/*z*: (pos.) 217 $[M+Na]^+$. FAB-HRMS *m*/*z*: 217.0684 ($C_7H_{14}O_6Na$ requires 217.0688). ^1H and ^{13}C NMR spectroscopic properties of **11** were in accord with those of the product obtained by alkaline degradation of kotalanol (**2**).

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