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ORIGINAL PAPER

Synthesis of 2-acetyl-5-(1,2,3,4,5,6-hexahydroxyhexyl)thiazoles

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Abstract The syntheses of two diastereoisomers of 2-acetyl-5-(1,2,3,4,5,6-hexahydroxyhexyl)thiazole are reported. The synthesis of these diastereoisomers involved the coupling of 5-metallated 2-(1,1-dimethoxyethyl)thiazole with a Weinreb amide derived from δ-gluconolactone, followed by asymmetric reduction of the ketone thus prepared. The stereochemistries and structures of some key compounds were determined by single-crystal X-ray structural analysis.

Keywords THI analogues · Immunosuppressive agent · Asymmetric reduction · Thiazole derivatives · Hexahydroxy side chain

Introduction

As part of a medicinal chemistry project [1–6] we required the synthesis of the 4- and 5-thiazole analogues, **2**, **3**, and **4** respectively, of the known immunosuppressive agent (1*R*,2*S*,3*R*)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI, **1**) [7–9]. THI is a minor component of the common food additive Caramel Colour III. THI caused lymphopenia (depression of blood lymphocyte counts), without any apparent side-effects, in mice and rats that were given THI in their drinking water [7, 8]. Thus THI and its analogues have potential applications as an immunosuppressive agent in organ transplant biology or for preventing the onset of diabetes [9].

The synthesis of thiazole analogues of THI such as compounds **2** ($n = 1, 2$) and **3** ($n = 1, 2$) was previously reported by us [10]. We now report the details of the synthesis of two of the more extended side-chain diastereoisomers of the hexahydroxyhexyl analogues **4**, as shown in Fig. 1, and their X-ray structures to support their stereochemical assignments. Our first strategy was to introduce the hexahydroxyhexyl side chain with the stereochemistries of (1*R* or 1*S*, 2*R*, 3*S*, 4*R*, 5*R*) onto the thiazole ring at the 5-position. This involved the coupling of 5-metallated 2-(1,1-dimethoxyethyl)thiazole (**10**) with the novel Weinreb amide **8** to provide ketone **11**, then asymmetric reduction of the ketone to provide two diastereomers **12** and **13** of the hexahydroxyhexyl thiazoles.

Results and discussion

Compound **8** was prepared from δ-gluconolactone (**5**), using a known procedure [11, 12] to provide triisopropylidene-D-gluconate **6** (Scheme 1). The structure of compound **6** was confirmed by single-crystal X-ray analysis (Fig. 2).

Compound **6** was then heated in the presence of morpholine in a sealed tube at 100 °C to afford the hydroxy amide **7** in 95% yield. The hydroxy amide **7** was then protected as the *tert*-butyldimethylsilyl ether which provided **8** in 97% yield. Single-crystal X-ray structural

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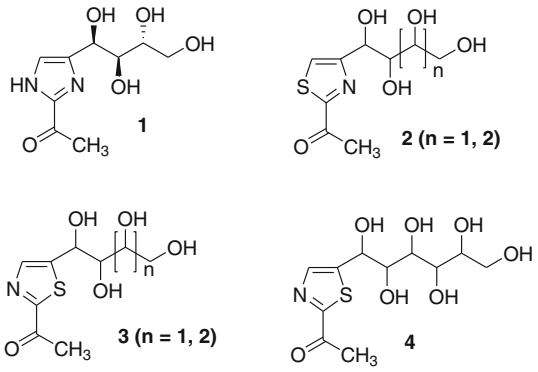
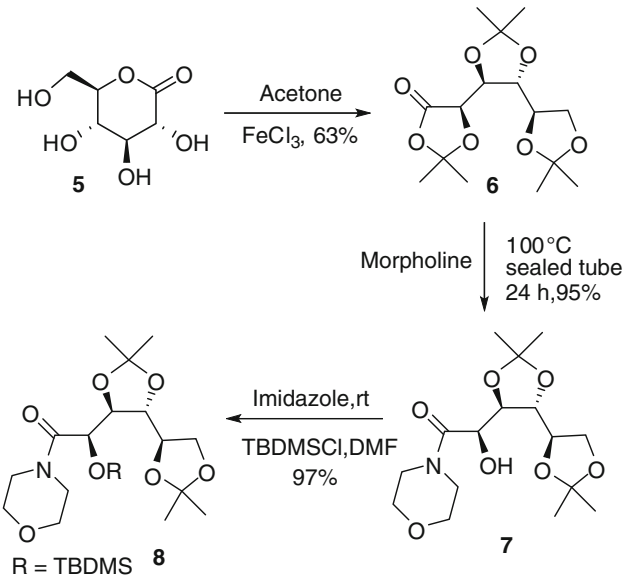


Fig. 1 THI (**1**) and its thiazole analogues (**2**–**4**)



Scheme 1

analysis of **8** further confirmed the structure elucidation by NMR analysis. The X-ray structure of compound **8** is shown (Fig. 3) to have the same absolute configuration as **5**. The $SiMe_2t$-Bu 'tail' is disordered (occupancies: 0.852(2) and complement).

Commercially available 2-acetylthiazole (**9**) was converted to its dimethoxyketal **10** in 80% yield, using previously reported reaction conditions [10]. The 5-lithiothiazole derivative of **10** was generated at −78 °C and was coupled with Weinreb amide **8** at the same temperature and then at room temperature for 2 h to give **11** in 63% yield with recovery of starting materials (Scheme 2).

The presence of the downfield singlet in the ^{1}H NMR spectrum of **11** at 8.7 ppm indicated the presence of the coupled thiazole (H4). A suitable crystal of **11** was obtained and analysed by single-crystal X-ray analysis to give the structure, as shown in Fig. 4.

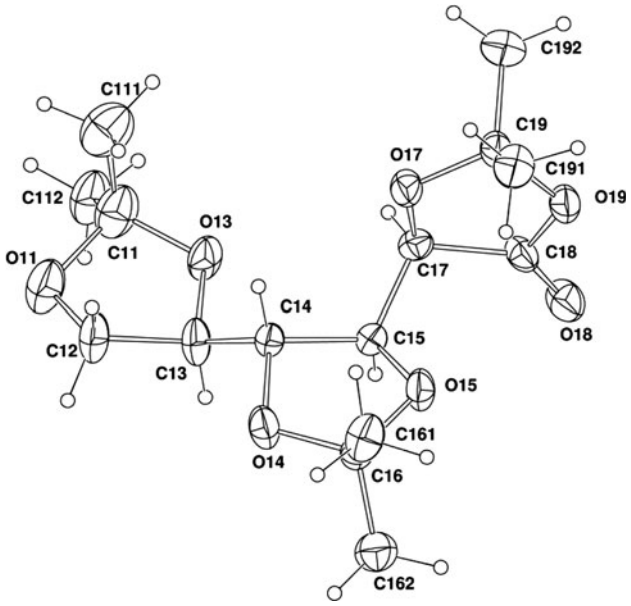


Fig. 2 X-ray structure of compound **6**

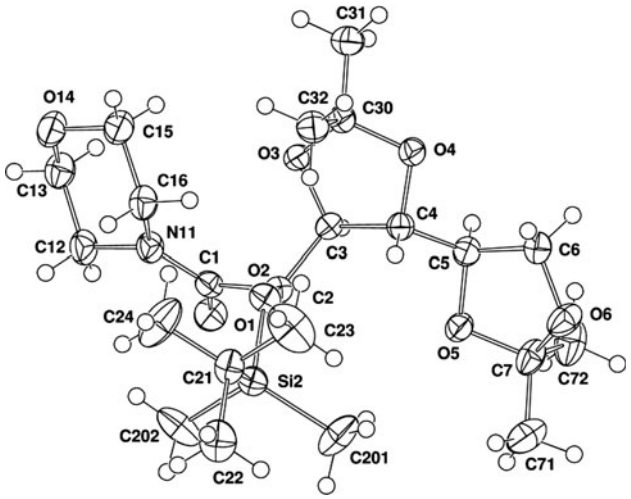
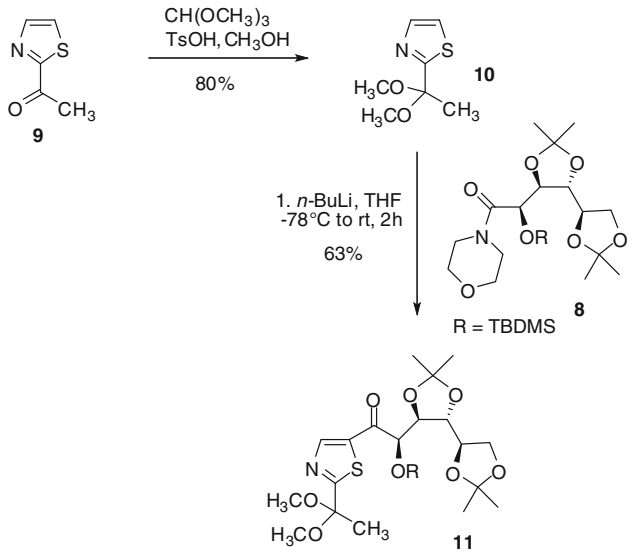
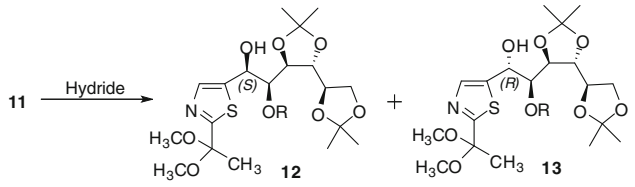


Fig. 3 X-ray structure of compound **8**

Reduction of ketone **11** with diisobutylaluminium hydride (DIBAL) in anhydrous diethyl ether at −78 °C gave exclusively the *syn*-**12** isomer in 90% yield (Scheme 3). When the reaction was carried out at 0 °C using sodium borohydride, a mixture of isomers **12** and **13** (1*S*/1*R* = 13:87) was produced in 86% yield. Both K- and L-Selectride were also used at −78 °C to produce mixtures of isomers (**12**/**13** = 18:82, 83% yield) and (**12**/**13** = 17:83, 88% yield), respectively. The results of the reduction of ketone **11** with various reducing agents and suggested transition states are listed in Table 1. The difference in stereoselectivity is due to the various transition states involved in the transformations which will be discussed later in this paper.



Scheme 2



Reducing agent	dr (**12**:**13**)
DIBAL	100 : 0
$NaBH_4$	13 : 87
K-Selectride	18 : 82
L-Selectride	17 : 83

Scheme 3

When using DIBAL as the reducing agent at room temperature, it was possible to obtain a 1:1 mixture of the *syn*-**12** and *anti*-**13** isomers. This allowed an excellent comparison of the ^{1}H NMR data for the two isomers and afforded both isomers for spectroscopic characterization and future biological testing.

The stereochemistry of the major isomer **12** was unequivocally determined by single-crystal X-ray crystallography as shown in Fig. 5, confirming the structure of compound **12** with the correct absolute configuration.

The stereochemistry of the major isomer **12** is that predicted by the Felkin–Anh transition model **A** [13–18] (Fig. 6), showing that the hydride attack between the small and medium sized groups (where the OTBDMS group is considered as the large group) at an angle of approximately 107° to the carbonyl oxygen would give rise to the *syn*-isomer, as described by Dondoni et al. [16–18] in relation to the reductions of related thiazolyl ketones. Similarly, the typical β-chelation transition state **B** results in the formation of *syn*-isomer. Indeed, it was further found that with sodium borohydride and both K- and L-Selectride, the major product was the *syn*-isomer. The *anti*-isomer **13** would be expected from the α-chelation model **C** (Fig. 6).

Table 1 Results of the reduction of ketone **11** with various reducing agents and suggested transition states

Reagent	Yield (%)	Ratio *syn*-**12**/*anti*-**13**	Transition state
DIBAL/−78 °C	90	100:0	β-Chelation
$NaBH_4$/0 °C	86	13:87	Felkin–Ahn
L-Selectride/ −78 °C	88	17:83	Felkin–Ahn
K-Selectride/ −78 °C	83	18:82	Felkin–Ahn

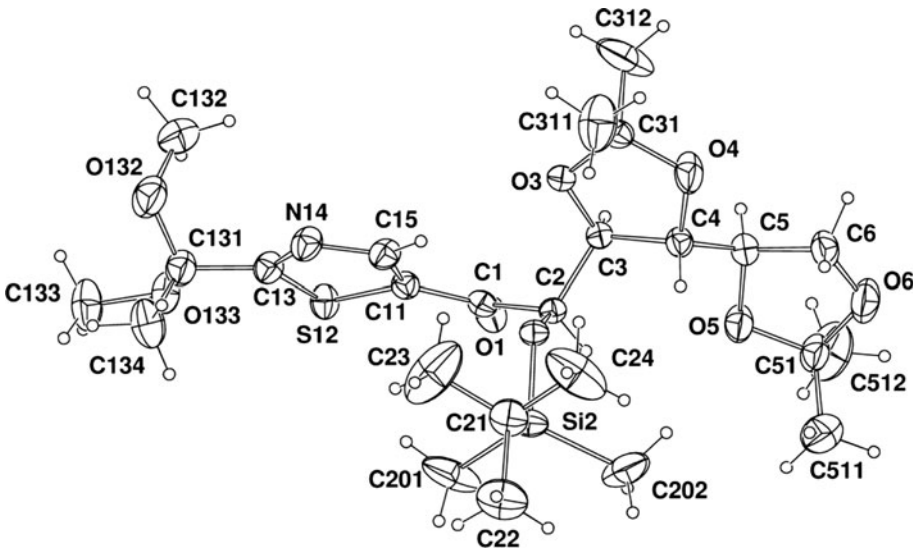


Fig. 4 X-ray structure of compound **11**

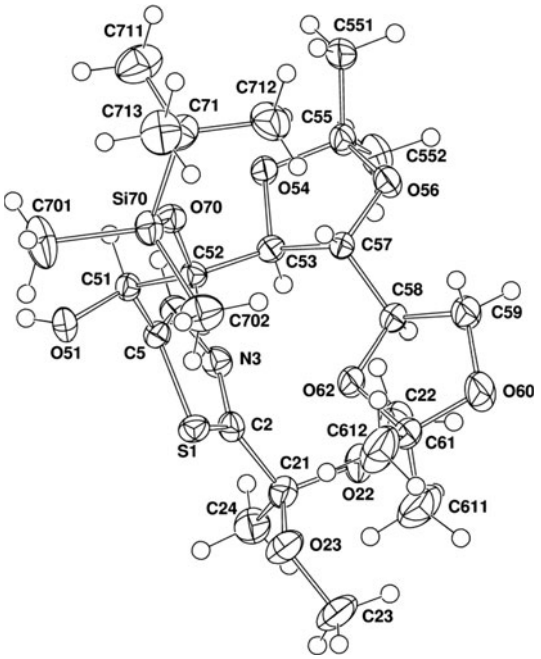
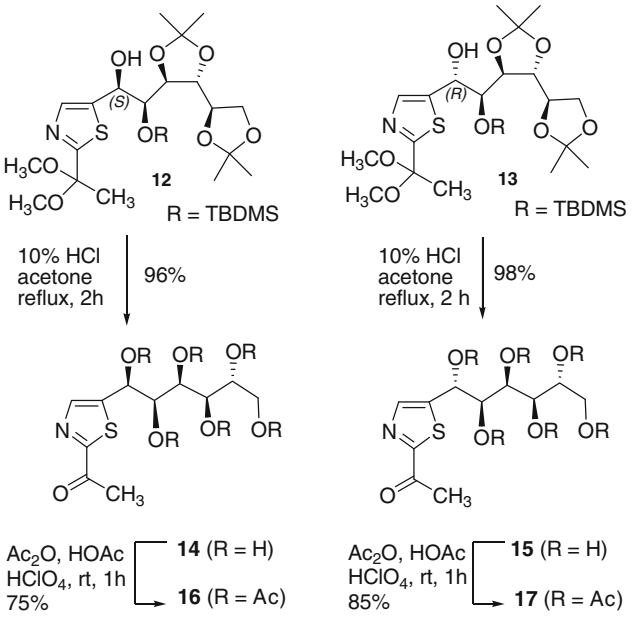


Fig. 5 X-ray structure of compound **12**



Scheme 4

This transition state is less favoured because of the steric hindrance of the bulky TBDMS group [19].

The protected hexols **12** and **13** were individually hydrolysed in 10% HCl/acetone (1:1) by heating at reflux for 2 h to give the desired hexols **14** and **15**, respectively, as hydrochloride salts. These compounds were isolated as clear yellow oils in 98 and 96% yields for the *syn*- (**14**) and *anti*-isomers (**15**) respectively, as shown in Scheme 4.

The ^{1}H NMR spectra of hexols **14** and **15** were very similar but not identical. In order to confirm the identity of these compounds, it was necessary to synthesise the hexaacetate derivatives of both isomers. The hexaacetates **16** (*syn*-isomer) and **17** (*anti*-isomer) were obtained in yields of 75 and 85% respectively after purification by preparative TLC (Scheme 4).

In summary two novel hexahydroxyhexyl side chain thiazole analogues (**12** and **13**) of THI were synthesized in a stereochemically defined manner. The stereochemistry of the compounds was determined from a combination of ^{1}H NMR analysis and X-ray structural analysis. In the case of δ-gluconolactone (**5**), the conversion to amide functionality in the form of the Weinreb amide **8** served this purpose admirably, allowing access to analogues not available under the generic methodology. The use of carbohydrates such as **5** as starting materials allowed the incorporation of the desired stereochemistry in the final products. Biological activities of these compounds will be determined and reported at a later stage.

Experimental

General procedures were as described previously [1, 3, 6]. Unless otherwise indicated, all NMR spectra were recorded in $CDCl_3$ solution, using tetramethylsilane (TMS) as an

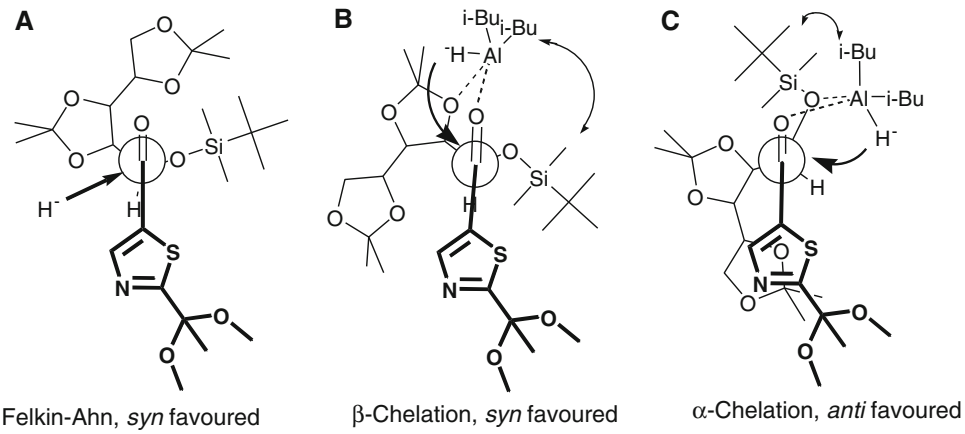


Fig. 6 Transition state models used to rationalise the diastereoselectivity of the asymmetric reduction of ketone **11**

internal standard at 300 MHz (^{1}H NMR) or 77.5 MHz (^{13}C NMR). 2-Acetylthiazole and δ-gluconolactone were purchased from Sigma-Aldrich. Compounds **6** [12] and **10** [10] were prepared following known procedures.

N-(3,4:5,6-Di-O-isopropylidene-2R,3S,4R,5R,6-pentahydroxy-1-oxohexyl)morpholine (**7**, $C_{16}H_{27}NO_7$)
1,2:3,4:5,6-Tri-*O*-isopropylidene-δ-gluconolactone (**6**, 1.00 g, 3.16 mmol) and 1.03 g morpholine (1.01 cm^3, 11.86 mmol, 3.75 eq) were combined in a sealed tube and heated to 100 °C for 24 h, after which the reaction was allowed to cool to room temperature. The solution was diluted with 25 cm^3 dichloromethane and washed with 0.1 M hydrochloric acid. The aqueous washings were extracted with dichloromethane (3 × 15 cm^3) and all organic fractions were combined. After washing with distilled water (3 × 50 cm^3) and drying over magnesium sulfate, the organic fraction was concentrated in vacuo to yield compound **7** (1.04 g, 95%) as a yellow syrup. ^{1}H NMR: δ = 4.59 (dd, 1H, J = 1.1, 9.3 Hz, H2′), 4.18 (m, 1H, H3′), 4.08 (m, 1H, H6a′), 4.06 (m, 1H, H5′), 4.00 (m, 1H, H6b′), 3.97 (m, 1H, H4′), 3.79 (d, 1H, J = 9.3 Hz, OH2′), 3.75–3.45 (br m, 8H, 2(O–CH$_2$) and 2(NCH$_2$)), 1.44 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$), 1.39 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$) ppm; ^{13}C NMR: δ = 170.2 (C), 110.6 (C), 109.5 (C), 80.4 (CH), 77.5 (CH), 77.4 (CH), 68.0 (CH$_2$), 66.6 (OCH$_2$), 66.2 (OCH$_2$), 66.2 (CH), 45.4 (N–CH$_2$), 42.8 (N–CH$_2$), 27.1 (CH$_3$), 26.5 (CH$_3$), 26.3 (CH$_3$), 25.1 (CH$_3$) ppm; HRMS (CI): calculated for $C_{16}H_{27}NO_7$ (MH^+) 345.1788, found 345.1787.

N-(2-O-tert-Butyldimethylsilyl-3,4:5,6-di-O-isopropylidene-2R,3S,4R,5R,6-pentahydroxy-1-oxohexyl)morpholine (**8**, $C_{22}H_{41}NO_7Si$)
The alcohol **7** (1.10 g, 3.19 mmol) was dissolved in anhydrous 15 cm^3 dimethyl formamide (DMF). While stirring at room temperature, 1.30 g imidazole (19.1 mmol, 6.4 eq) was added and allowed to dissolve before the addition of 0.80 g *tert*-butyldimethylsilyl chloride (6.9 mmol, 2.35 eq). The reaction mixture was then stirred at 40 °C for 72 h before being poured into 100 cm^3 diethyl ether and washed with 50 cm^3 0.5 M hydrochloric acid. The aqueous fraction was back extracted with diethyl ether (3 × 50 cm^3). The combined organic fractions were washed with saturated sodium chloride (3 × 50 cm^3), dried over magnesium sulfate, and the solvent was removed under reduced pressured to yield a white solid. Recrystallisation from petroleum ether gave **8** (1.426 g, 97%) as large colourless crystals. M.p.: 64–66 °C; ^{1}H NMR: δ = 4.53 (d, 1H, J = 2.5 Hz, H2′), 4.30 (br m, 1H, morpholine), 4.19 (dd, 1H, J = 2.5, 7.2 Hz, H3′), 4.14 (dd, 1H, J = 6.1, 8.1 Hz, H6a′), 4.04 (ddd, 1H, J = 6.1, 7.0, 7.8 Hz, H5′), 4.02 (m, 1H, morpholine), 3.96 (dd, 1H, J = 7.2, 7.8 Hz, H4′), 3.78 (dd, J = 7.0, 8.1 Hz, H6b′), 3.76–3.5 (br m, 5H, morpholine), 3.20 (br m, 1H, morpholine), 1.39 (s, 3H, CH$_3$), 1.36 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$), 0.92 (s, 9H, C(CH$_3$)$_3$), 0.10 (s, 3H, SiCH$_3$), 0.07 (s, 3H, SiCH$_3$) ppm; ^{13}C NMR: δ = 169.7 (C), 109.8 (C), 109.7 (C), 81.9 (CH), 77.1 (CH), 76.9 (CH), 75.7 (CH), 67.9 (CH$_2$), 67.1 (CH$_2$), 66.8 (CH$_2$), 46.3 (CH$_2$), 43.0 (CH$_2$), 27.1 (CH$_3$), 26.6 (CH$_3$), 26.3 (CH$_3$), 25.6 (3CH$_3$), 25.1 (CH$_3$), 18.0 (C), −5.0 (CH$_3$), −5.6 (CH$_3$) ppm; HRMS (ESI): calculated for $C_{22}H_{42}NO_7Si$ (MH^+) 460.2730, found 460.2730.

2-(1,1-Dimethoxyethyl)-5-(2-O-tert-butyldimethylsilyl-3,4:5,6-di-O-isopropylidene-2R,3S,4R,5R,6-pentahydroxy-1-oxohexyl)thiazole (**11**, $C_{25}H_{43}NO_8SSi$)
2-(1,1-Dimethoxyethyl)thiazole (**10**, 1 g, 5.77 mmol, 1.17 eq) was dissolved in 15 cm^3 dry tetrahydrofuran (THF) and cooled to −78 °C under a nitrogen atmosphere. *n*-BuLi (7.52 mmol, 4.7 cm^3 of 1.6 M, 1.52 eq) was slowly added and the mixture was stirred at −78 °C for 30 min before the addition of a solution of 2.27 g **8** (4.94 mmol) in 15 cm^3 dry THF. The reaction was stirred under N_2 atmosphere while warming to room temperature over 2 h, and then poured into 30 cm^3 saturated ammonium chloride solution. The aqueous fraction was extracted with dichloromethane (3 × 30 cm^3). The combined dichloromethane extracts were washed with a saturated solution of sodium chloride (3 × 30 cm^3) and dried over magnesium sulfate before concentrating in vacuo. Recrystallisation from diethyl ether yielded **11** (1.055 g, 37%) as clear colourless crystals. The starting material **8** (765 mg) was also recovered by recrystallisation, in successive crystallisations of this same solution. This gave an overall yield of 63% of the title compound taking into account the recovered starting material. M.p.: 102–105 °C; ^{1}H NMR: δ = 8.66 (s, 1H, H4), 4.63 (d, 1H, J = 2.2 Hz, H2′), 4.25 (m, 1H, J = 2.2 Hz, H3′), 4.19 (m, 1H, J = 8.2 Hz, H6′), 4.05 (m, 2H, H4′ and H5′), 3.84 (m, 1H, J = 8.2 Hz, H6′), 3.28 (s, 3H, OCH$_3$), 3.24 (s, 3H, OCH$_3$), 1.73 (s, 3H, ThCCH$_3$), 1.49 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$), 0.9 (s, 9H, *t*-butyl), 0.10 (s, 3H, SiCH$_3$), −0.08 (s, 3H, SiCH$_3$) ppm; ^{13}C NMR: δ = 194.1 (C), 178.4 (C), 150.0 (C), 137.4 (CH), 110.7 (C), 109.8 (C), 100.9 (C), 82.3 (CH), 78.6 (CH), 77.4 (CH), 77.3 (CH), 68.3 (CH$_2$), 49.5 (CH$_3$), 49.5 (CH$_3$), 27.3 (CH$_3$), 26.7 (CH$_3$), 26.4 (CH$_3$), 25.8 (CH$_3$), 25.1 (CH$_3$), 23.9 (CH$_3$), 18.2 (C), −4.7 (CH$_3$), −5.1 (CH$_3$) ppm; HRMS (CI +): calculated for $C_{25}H_{44}NO_8SSi$ (MH^+) 546.2512, found 546.2557.

2-(1,1-Dimethoxyethyl)-5-(2-O-tert-butyldimethylsilyl-3,4:5,6-di-O-isopropylidene-1S,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**12**, $C_{25}H_{45}NO_8SSi$)
To a stirred solution of 230 mg ketone **11** (0.42 mmol) in 5 cm^3 anhydrous diethyl ether at −78 °C was added dropwise a solution of diisobutylaluminium hydride

(0.69 mmol). Stirring was continued for 1 h after which the reaction was quenched with 5 cm^3 methanol. A saturated solution of potassium tartrate (5 cm^3) was added and the reaction stirred for 1.5 h. The organic phase was collected and the remaining aqueous phase extracted with diethyl ether (3 × 10 cm^3). The combined organic extracts were washed with a saturated solution of sodium bicarbonate and then distilled water, followed by drying over magnesium sulfate. Concentration in vacuo yielded solely the (1*S*)-alcohol **12** (208 mg, 90.1%) as clear colourless crystals. M.p.: 97–99 °C; ^{1}H NMR: $\delta = 7.67$ (1H, s, H4), 5.17 (ddd, 1H, $J = 1.1$, 2.8, 6.4 Hz, H1′), 4.15 (dd, 1H, $J = 6.0$, 8.3 Hz, H3′), 4.00 (m, 4H, H2′, H5′, H6a′, H6b′), 3.88 (dd, 1H, $J = 6.3$, 8.3 Hz, H4′), 3.49 (d, 1H, $J = 6.4$ Hz, OH1′), 3.25 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 1.69 (s, 3H, $ThCCH_3$), 1.42 (s, 3H, $OCCH_3$), 1.41 (s, 3H, $OCCH_3$), 1.34 (s, 3H, $OCCH_3$), 1.32 (s, 3H, $OCCH_3$), 0.83 (s, 9H, *t*-butyl), 0.09 (s, 3H, $SiCH_3$), −0.12 (s, 3H, $SiCH_3$) ppm; ^{13}C NMR: $\delta = 171.2$ (C), 141.8 (C), 139.3 (CH), 109.9 (C), 109.3 (C), 101.0 (C), 81.5 (CH), 78.0 (CH), 77.3 (CH), 77.1 (CH), 68.8 (CH), 67.8 (CH_2), 49.4 (CH_3), 49.4 (CH_3), 27.0 (CH_3), 26.9 (CH_3), 26.3 (CH_3), 25.9 (CH_3), 25.2 (CH_3), 24.2 (CH_3), 18.4 (C), −4.0 (CH_3), −4.8 (CH_3) ppm; HRMS (CI): calculated for $C_{25}H_{46}NO_8SSi$ (MH^+) 548.2713, found 548.2713.

2-(1,1-Dimethoxyethyl)-5-(2-O-tert-butyldimethylsilyl-3,4:5,6-di-O-isopropylidene-1S,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**12**, $C_{25}H_{45}NO_8SSi$)
and 2-(1,1-dimethoxyethyl)-5-(2-O-tert-butyldimethylsilyl-3,4:5,6-di-O-isopropylidene-1R,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**13**, $C_{25}H_{45}NO_8SSi$)

To a stirred solution of 200 mg ketone **11** (0.366 mmol) in 10 cm^3 anhydrous methanol at 0 °C was added 70 mg sodium borohydride (1.85 mmol, 5 eq) over 1 h. The reaction was stirred until TLC analysis (15% ethyl acetate in hexane on silica gel) indicated completion, after which the reaction was quenched with 10 cm^3 saturated solution of ammonium chloride. The reaction was extracted with dichloromethane (3 × 20 cm^3) and the organic fractions combined before washing with saturated sodium chloride solution and drying over magnesium sulfate. Concentration in vacuo yielded a mixture of the (1*S*)- and (1*R*)-diastereomeric alcohols **12** and **13** (172 mg, 86%) as a pale yellow solid (**12/13** = 13:87). Recrystallisation of the mixture from 1:5 ethyl acetate/petroleum ether separated the alcohols **12** and **13** into white crystals and a white powdery solid, respectively.

Compound **13**: ^{1}H NMR: δ = 7.67 (s, 1H, H4), 5.04 (d, 1H, $J = 5.1$ Hz, H1′), 4.07 (dd, 1H, $J = 5.6$, 8.6 Hz, H3′), 3.96 and 3.88 (2 m, 4H, H4′, H5′, H6a′, H6b′), 3.79 (ddd, 1H, $J = 1.1$, 5.6 Hz, 8.1, H2′), 3.24 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 2.74 (d, 1H, $J = 8.1$ Hz, OH), 1.72 (s, 3H, $ThCCH_3$), 1.37 (s, 3H, $OCCH_3$), 1.35 (s, 3H, $OCCH_3$), 1.30 (s, 3H, $OCCH_3$), 1.29 (s, 3H, $OCCH_3$), 0.83 (9H, s, *t*-butyl), 0.09 (3H, s, $SiCH_3$), −0.12 (3H, s, $SiCH_3$) ppm; ^{13}C NMR: $\delta = 172.3$ (C), 141.1 (C), 140.1 (CH), 110.1 (2C), 101.3 (C), 79.1 (CH), 78.0 (CH), 77.5 (CH), 73.6 (CH), 71.3 (CH), 68.2 (CH_2), 49.3 (CH_3), 49.2 (CH_3), 27.5 (CH_3), 27.1 (CH_3), 27.0 (CH_3), 26.1 (CH_3), 25.7 (CH_3), 24.4 (CH_3), 18. 5 (C), −4.4 (CH_3), −4.7 (CH_3) ppm; HRMS (CI+): calculated for $C_{25}H_{46}NO_8SSi$ (MH^+) 548.2713, found 548.2713.

Using L-Selectride: To a stirred solution of 36 mg ketone **11** (0.066 mmol) in 5 cm^3 dry THF at −78 °C was added a solution of L-Selectride (0.2 mmol, 3 eq). After stirring for 4 h the reaction was quenched with a solution of 10% sodium hydroxide and 30% hydrogen peroxide (2:1, 5 cm^3). The reaction was stirred at room temperature for 2 h, then diluted with 10 cm^3 saturated sodium chloride solution and extracted with ethyl acetate (3 × 20 cm^3). The combined organic extracts were washed with distilled water and dried over magnesium sulfate. The solvent was removed to provide a diastereoisomeric mixture of the alcohols **12** and **13** (32 mg, 88%, 1*S*/1*R* = 17:83). The products had identical ^{1}H and ^{13}C NMR spectra to those seen above for the reduction reactions using sodium borohydride and diisobutylaluminium hydride.

Using K-Selectride: To a stirred solution of 36 mg ketone **11** (0.066 mmol) in 5 cm^3 dry THF at −78 °C was added a solution of K-Selectride (0.2 mmol, 3 eq). After stirring for 4 h the reaction was quenched with a solution of 10% sodium hydroxide and 30% hydrogen peroxide (2:1, 5 cm^3). The reaction was stirred at room temperature for 2 h, then diluted with 10 cm^3 saturated sodium chloride solution and extracted with ethyl acetate (3 × 20 cm^3). The combined organic extracts were washed with distilled water and dried over magnesium sulfate. The reaction yielded a diastereoisomeric mixture of the alcohols **12** and **13** (30 mg, 83%, 1*S*/1*R* = 18:82).

*General synthesis procedure for **14** and **15***

The alcohol **12** or **13** (31 mg, 0.056 mmol) was dissolved in 5 cm^3 of a 1:1 mixture of acetone and 10% hydrochloric acid solution and the reaction mixture was heated at reflux for 2 h. The acetone was removed in vacuo and the aqueous phase washed with diethyl ether, before the remaining water was removed in vacuo to yield the hexol products **14** or **15**, respectively.

2-Acetyl-5-(1S,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**14**, $C_{11}H_{17}NO_7S$)

Yield 96%; dark yellow oil; ^{1}H NMR (D_2O): $\delta = 7.80$ (s, 1H, H4), 5.09 (d, 1H, H1′), 3.75–3.35 (m, 6H, H2′–H6a′ and H6b′), 2.48 (s, 3H, CH_3) ppm; ^{13}C NMR (D_2O): $\delta = 192.69$ (C), 165.07 (C), 149.20 (C), 139.95 (CH), 74.72 (CH), 72.64 (CH), 71.15 (CH), 71. 02 (CH), 68.18

(CH), 64.41 (CH_2), 25.27 (CH_3) ppm; HRMS (ESI): calculated for $C_{11}H_{18}NO_7S$ (MH^+) 308.0799, found 308.0800.

2-Acetyl-5-(1R,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**15**, $C_{11}H_{17}NO_7S$)
Yield 98%; dark yellow oil; ^{1}H NMR (D_2O): $\delta = 7.74$ (s, 1H, H4), 5.08 (d, 1H, $J = 2.3$ Hz, H1′), 3.87 (dd, 1H, $J = 2.3$, 7.8 Hz, H2′), 3.80–3.67 (m, 2H, H3′ and H4′), 3.65 (dd, 1H, $J = 2.8$, 11.9 Hz, H5b′), 3.52 (dd, 1H, $J = 7.0$, 11.9 Hz, H5a′), 2.54 (s, 3H, CH_3) ppm; ^{13}C NMR (D_2O): $\delta = 193.36$ (C), 165.28 (C), 145.76 (C), 141.95 (CH), 74.06 (CH), 72.64 (CH), 71.25 (CH), 70.98 (CH), 67.78 (CH), 64.31 (CH_2), 25.28 (CH_3) ppm; HRMS (ESI): 308.0797 calculated for $C_{11}H_{18}NO_7S$ (MH^+) 308.0799, found 308.0797.

*General synthesis procedure for **16** and **17***
To a stirred solution of 3 cm^3 acetic anhydride and 5 cm^3 glacial acetic acid was added the hexol **14** or **15** (45 mg, 0.146 mmol). A perchloric acid/acetic anhydride catalyst (1 g of 70% perchloric acid in 2.3 g acetic anhydride) was added (4 drops) and the mixture stirred for 1 h before pouring into 20 cm^3 ice-water. The mixture was then extracted with ethyl acetate (3 × 30 cm^3). The combined ethyl acetate extracts were dried over magnesium sulfate and concentrated in vacuo. Purification using semi-preparative TLC using silica gel plates with 15% ethyl acetate in hexanes as the eluent yielded the hexaacetate product.

2-Acetyl-5-(1,2,3,4,5,6-hexa-O-acetyl-1S,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**16**, $C_{23}H_{28}NO_{13}S$)
Yield 75%; pale yellow oil; ^{1}H NMR: δ = 7.91 (s, 1H, H5), 6.34 (d, 1H, $J = 3.9$ Hz, H1′), 6.01 (m, 1H, H4′), 5.87 (dd, 1H, $J = 3.7$, 6.8 Hz, H3′), 5.58 (dd, 1H, $J = 3.9$, 6.8 Hz, H2′), 5.49 (m, 1H, $J = 3.35$, 7.6 Hz, H5′), 4.41 (dd, 1H, $J = 3.35$, 11.9 Hz, H6a′), 4.14 (dd, 1H, $J = 7.6$, 11.9 Hz, H6b′), 2.72 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.08 (s, 6H, $2CH_3$), 2.07 (s, 3H, CH_3), 2.04 (s, 6H, $2CH_3$) ppm; HRMS (CI): caculated for $C_{23}H_{29}NO_{13}S$ (MH^+) 559.1351, found 559.1351.

2-Acetyl-5-(1,2,3,4,5,6-hexa-O-acetyl-1R,2R,3S,4R,5R,6-hexahydroxyhexyl)thiazole (**17**, $C_{23}H_{28}NO_{13}S$)
Yield 85%; pale yellow oil; ^{1}H NMR: δ = 7.87 (s, 1H, H5), 6.23 (d, 1H, $J = 4.2$ Hz, H1′), 6.06 (1H, m, $J = 3.4$ Hz, H4′), 5.81 (dd, 1H, $J = 3.4$, 7.0 Hz, H3′), 5.67 (dd, 1H, $J = 4.2$, 7.0 Hz, H2′), 5.41 (m, 1H, $J = 2.9$, 6.3 Hz, H5′), 4.39 (dd, 1H, $J = 2.9$, 11.1 Hz, H6a′), 4.15 (dd, 1H, $J = 6.3$, 11.1 Hz, H6b′), 2.74 (s, 3H, CH_3), 2.11 (s, 6H, $2CH_3$), 2.10 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.06 (s, 6H, $2CH_3$) ppm; HRMS (CI): calculated for $C_{23}H_{29}NO_{13}S$ (MH^+) 559.1351, found 559.1349.

*X-ray data for **6**, **8**, **11**, and **12***
The crystallographic data for the structures **6**, **8**, **11**, and **12** reported in this paper have been deposited at the Cambridge Structural Data Centre under CCDC numbers: 773751 (**6**), 773752 (**8**), 773753 (**11**), 773754 (**12**). The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

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