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Synthesis of thiazole analogues of the immunosuppressive agent (1R,2S,3R)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole

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Abstract

The synthesis of four of the diastereoisomers of 2-acetyl-5-(1,2,3,4-tetrahydroxybutyl)thiazole and two of the diastereoisomers of 2-acetyl-5-(1,2,3,4,5-pentahydroxypentyl)thiazole and 2-acetyl-4-(1,2,3,4,5-pentahydroxypentyl)thiazole are reported. These syntheses involve the condensation of 5- or 4-metallated 2-(1,1-dimethoxyethyl)thiazoles with 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone or 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribonolactone followed by reductive ring-opening of the resulting lactols. The stereochemistries and structures of some key compounds have been determined by single crystal X-ray structural analysis.

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Synthesis of 5-(1,2,3,4,5,6-hexahydroxhexyl)thiazole analogues of the immunosuppressive agent (1*R*, 2*S*, 3*R*)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole

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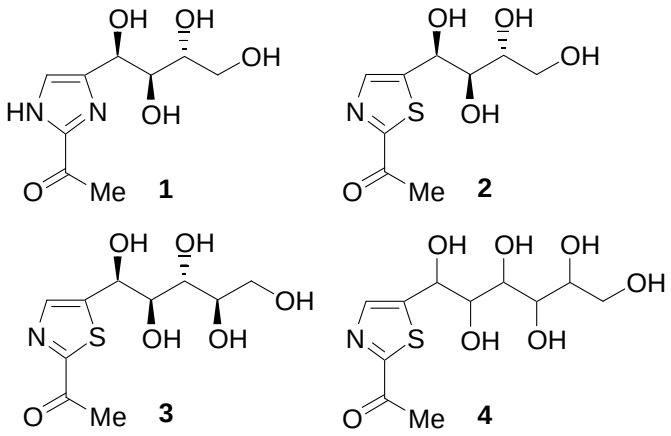
Summary: The synthesis of four of the diastereoisomers of 2-acetyl-5-(1,2,3,4,5,6-hexaahydroxyhexyl)thiazole are reported. These syntheses involve the condensation of 5-lithiated-2-(1,1-dimethoxyethyl)-thiazole with a *N*-acyl morpholine derivative of g-gluconolactone or 2,3:5,6-Di-*O*-isopropylidene-mannolactone followed by hydride reduction of the resulting ketone and lactol, respectively. The stereochemistries and structures of some key compounds have been determined by single crystal X-ray structural analysis.

Introduction

As part of an ongoing medicinal chemistry project[1-7] we required the synthesis of some 5-hexahydroxyhexylthiazole analogues, **4**, of the known immunosuppressive agent, (1*R*, 2*S*, 3*R*)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) **1**.[8-10] THI is a

minor component of the common food additive Caramel Colour III. THI has been found to cause lymphopenia (depression of blood lymphocyte counts), without any apparent side-effects, in mice and rats that have been given THI in their drinking water.[8,9] Thus THI and its analogues have potential applications as an immunosuppressive agent in organ transplant biology or for preventing the onset of diabetes.[10] Our earlier studies showed that compound **2**, the 5-thiazole analogue of THI, had essentially the same activity versus concentration profile as THI in causing lymphopenia in mice, while the pentahydroxylpentyl derivative **3** showed a slightly higher activity at the same concentration.[8]

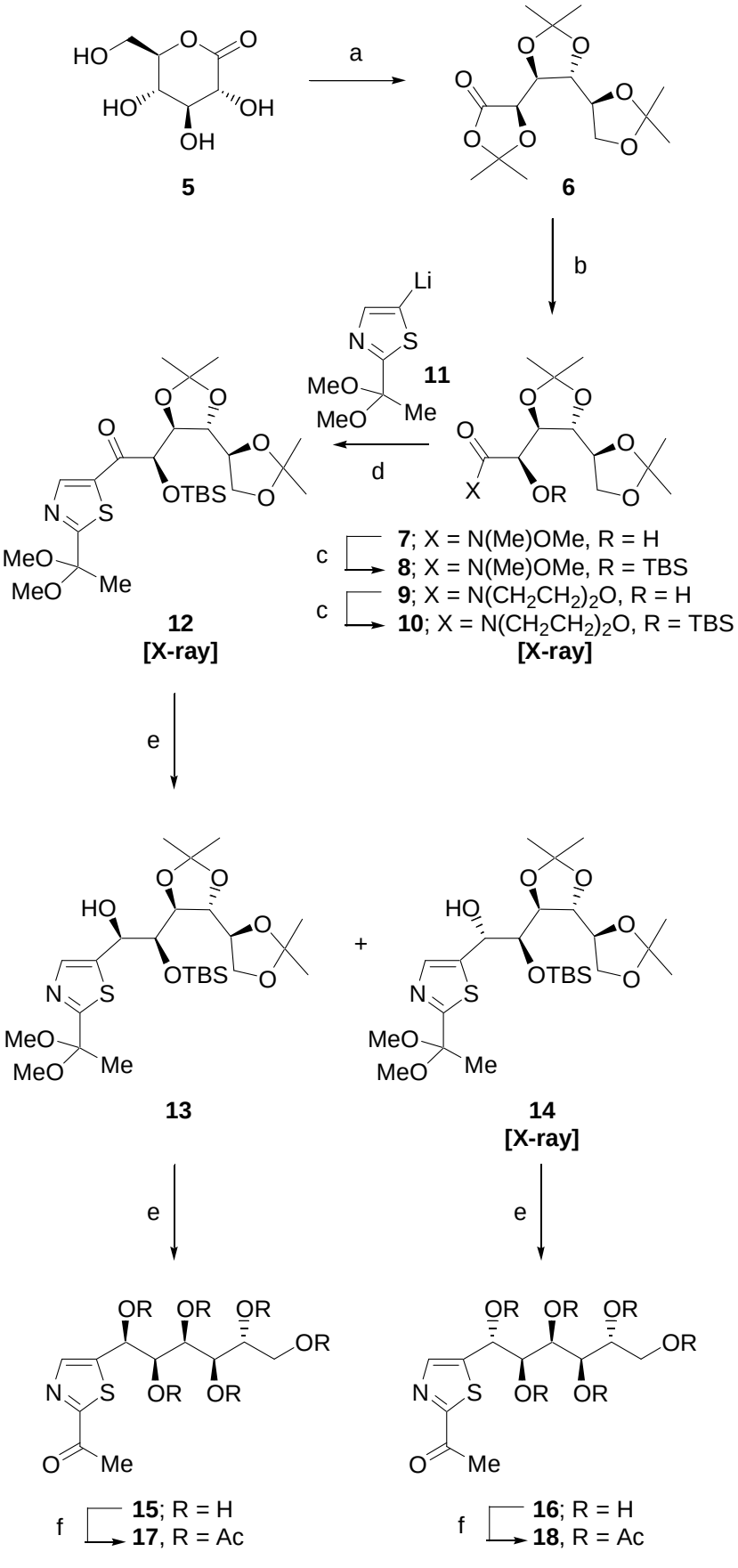


Results and Discussion

Our earlier strategy for the synthesis of 5-thiazole analogues of THI involves the condensation of 5-lithio-2-(1,1-dimethoxyethyl)-thiazole (**11**) with protected D-erythrono-1,4-lactone or D-ribonolactone followed by reductive ring-opening of the resulting lactols to give protected versions of the requisite analogues.[7] Attempts to condense the known dioxolanone?, 1,2:3,4:5,6-tri-*O*-isopropylidene-δ-gluconolactone **6**[11] with 5-lithio-2-(1,1-dimethoxyethyl)-thiazole[7] (THF, -78^{o}C to RT) gave no isolatable condensation products and only 2-(1,1-dimethoxyethyl)-thiazole could be recovered. We suspected that deprotonation of **6** α to the lactone carbonyl group was

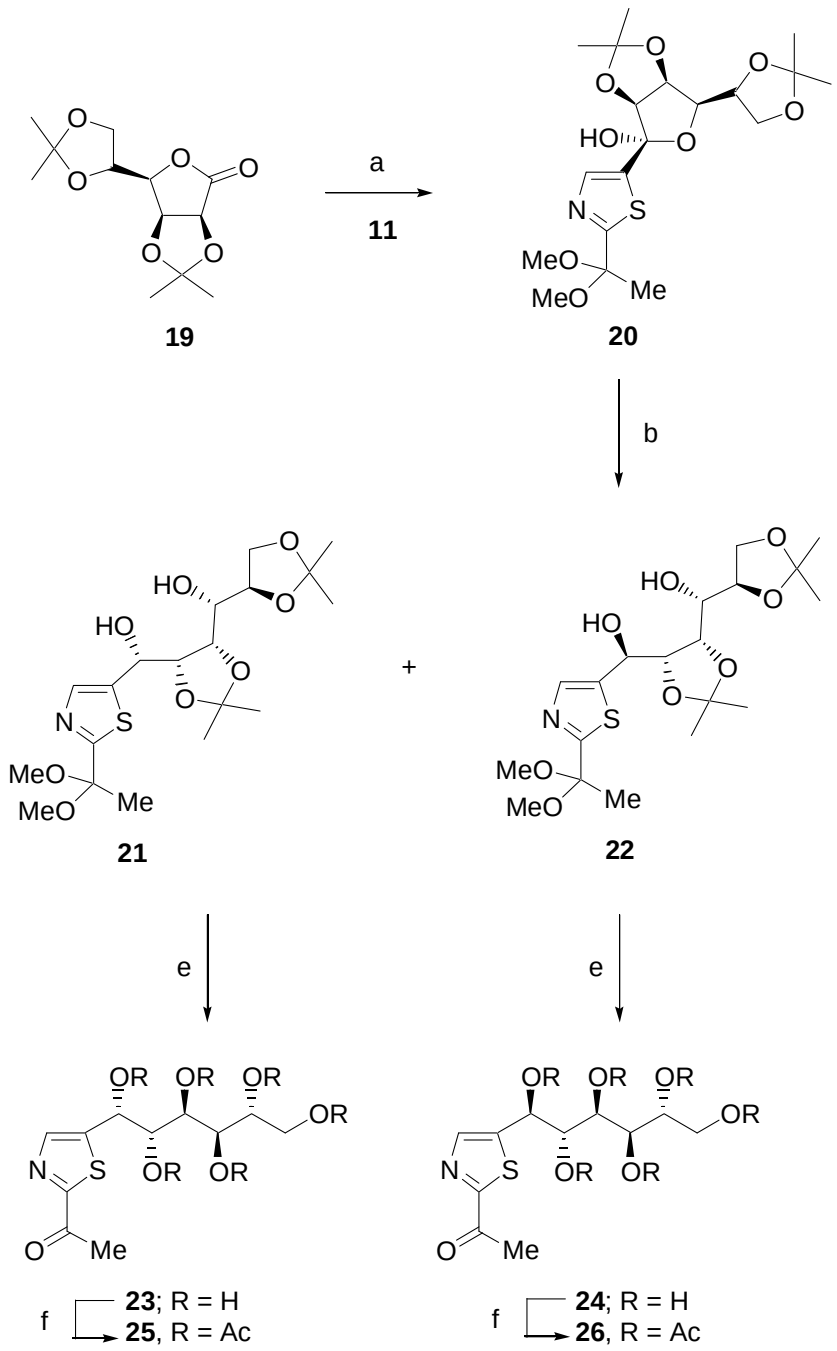
occurring followed by β-elimination of acetone to account for the lack of recovery of **6**. To this end dioxolanone **6** was treated with cholоromethylaluminium methoxymethylamine in benzene to yield the Wienreb-type amide derivative **7** in 75% yield which was converted to the TBS ether **8** under standard conditions. Treatment of **6** with an excess of morpholine (3.75 molar equiv) by heating in a sealed tube at 100^{o}C for 24 h gave the *N*-morpholine amide derivative **9** in 95% yield. The structure of the TBS derivative **10** of **9** was unequivocally demonstrated from a single-crystal X-ray analysis (Figure 1). Treatment of the *N*-methoxy,*N*-methylamide 8 with the 5-lithiothiazole **11** initially at –78 ^{o}C and then at RT for 2 h, followed by column chromatography, gave the ketone **12** in only 11% yield. The structure of this compound was secured by a single-crystal X-ray analysis (Figure 2). The reaction of **11** with the *N*-morpholine amide **10**, however was more successful and gave the ketone **12** in 37% purified yield or 67% based on recovered amide **10**.

Scheme 1


a
5
6
b
11
d
c
7; X = N(Me)OMe, R = H
8; X = N(Me)OMe, R = TBS
c
9; X = N(CH2CH2)2O, R = H
10; X = N(CH2CH2)2O, R = TBS
12
[X-ray]
[X-ray]
e
13
14
[X-ray]
e
e
f
15; R = H
17, R = Ac
f
16; R = H
18, R = Ac

Reduction of **10** with sodium borohydride in methanol at 0 ^{o}C afforded an 87 :13 mixture of the 1,2-*syn*- and 1,2-*anti*-products **13** and **14**respectively, that could not be readily separated by column chromatography. Fortunately pure *syn*-**13** could be obtained by recrystallization of a mixture of **13** and **14** from ethyl acetate / petroleum ether and its structure determined by single-crystal X-ray crystallographic analysis (Figure 3). The stereochemistry of the major alcohol **13** is that predicted by the Felkin-Anh transition model.[10-13] Similar diastereoselectivities were obtained when **12** was treated with L- or K-selectride (THF) at -78 ^{o}C. Treatment of a diethyl ether solution of **10** at -78 ^{o}C with precooled (-78 ^{o}C) DIBAL-H in diethyl ether was highly diastereoselective (dr >98 : <2) and gave essentially pure *anti*-product **14** in 90% yield. While an *anti*-product would be expected for reduction of an α-ether substituted ketone under chelation control the OTBS group is normally too hindered to participate in such a mechanism.[ref] Acid hydrolysis of the individual diastereoisomers **13** and **14** gave the hexaols **15** and **16**, respectively, that were converted to their corresponding hexa-acetates for further characterization.

Scheme 2 outlines the synthesis of the Reduction of the keto group of the 4-*O*-silylated *cis*-1,3-dioxolane **16** with a number of reducing agents ($NaBH_4$, DIBAL, Red-AL, K-selectride and L-selectride) gave mixtures of the diastereoisomeric alcohols **17** and **18**. The optimum diastereoselectivity was obtained (**17**:**18** = 84:16) when L-selectride was employed at –78 ^{o}C. The stereochemistry assigned to **17** was unequivocally determined by an X-ray study (Fig. 5) and is that expected from the Felkin-Ahn transition state model **D**. Acid hydrolysis of the individual diastereoisomers **17** and **18** gave the tetrols **19** and **20**, respectively.



Synthesis of 2-acetyl-4-(1,2,3,4,5-pentahydroxypentyl)- and 2-acetyl-5-(1,2,3,4,5-pentahydroxypentyl)-thiazoles

The 5-lithio thiazole derivative of **5** was treated with 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribonolactone **21**[15] at –78 °C for 1.5h to give the lactol **22**, as a single isomer in 64% yield (Scheme 4). In contrast to the corresponding reaction of lithiated **5** with lactone **6**, no ring-opening ketone products were observed. X-ray

analysis of **22** showed it had the same relative stereochemistry as **7b** with respect to the thiazole and 1,3-dioxolane rings (Fig. 6). Reduction of **22** with sodium borohydride in methanol at –10 ^{o}C afforded a mixture of the diols **23** and **24**. These could be isolated in diastereomerically pure form in 48% and 46% yields, respectively, by column chromatography. Attempts to reductively ring-open the lactol **22** with other reducing agents (e.g. DIBAL and L-selectride) were unsuccessful and only starting lactol **22** was recovered. The poor diastereoselectivity in the reduction of **22** is in stark contrast to that found for the lactol **7** and is unexpected based on the transition state structures **A** and **B**. The corresponding transition state structures **E** and **F** for the reduction of ring-opened **22** do not appear to be made unfavourable by the extra $TBSOCH_2$ group that should occupy a pseudo-equatorial position. Acid hydrolysis of the individual diastereoisomers **23** and **24** gave the pentols **25** and **26**, respectively, in good yields that were converted to their corresponding penta-acetates **27** and **28** respectively, under standard conditions.[4] The stereochemistry of **24** and **27** was confirmed by single crystal X-ray analysis (Fig. 7 and 8).

4-Bromo-2-(1,1-dimethoxyethyl)thiazole[6] underwent trans-metallation at –78 ^{o}C and was then treated with the lactone **21** at –78 ^{o}C for 1.5h (Scheme 5). Purification of the reaction mixture by column chromatography gave the desired lactol **29** (d. r. = 69:31) in 44% yield and surprisingly the isomeric 5-thiazole adduct **22** in 15% yield (Scheme 5). The latter compound must have arisen through formation of the more stable 5-lithiated thiazole derivative. Reduction of **29** with sodium borohydride in methanol at –10 ^{o}C afforded a 60:40 mixture of the diols **30** and **31**, respectively. Separation of this mixture by column chromatography gave diastereomerically pure **31** and **32** in 30% and 21% yields, respectively. The stereochemistry of **30** was secured by single crystal X-ray analysis (Fig. 9). Compounds **30** and **31** were converted to their pentols **32** and

33 respectively by acid hydrolysis. Small samples of these pentols were converted to their respective penta-acetates, **34** and **35**. The ^{1}H NMR analysis of the tetraacetate of THI (**1**) and its C1 epimer[4] and of the diastereomeric pairs **27** and **28** and **34** and **35** showed that H1, in compounds with the (1*R*)-stereochemistry (tetraacetate of **1**, **27** and **34**), comes further downfield of H1 in their respective isomers having the (1*S*)-stereochemistry. Furthermore, $J_{1,2}$ is generally smaller in the 1*R* diastereoisomer.

In conclusion, we have developed a short, efficient and diastereoselective synthesis of the (1*S*, 2*S*, 3*R*)- and (1*R*, 2*R* 3*R*)-5-thiazole analogues of the bioactive molecule THI from a common precursor, the lactol **3**. This methodology is complementary to the Sharpless asymmetric dihydroxylation method for the diastereoselective synthesis of the *syn*-1,2-diol moiety of THI and its analogues that have opposite stereochemistries at C-1 and C-2.[4,6] Extension of this methodology to prepare the pentahydroxylpentyl 4-thiazole and 5-thiazole analogues was also efficient but the diastereoselectivity of the reductive ring-opening steps were poorly diastereoselective. Furthermore, this approach should be applicable to the diastereoselective synthesis of other polyhydroxylated bioactive molecules. Preliminary experiments on these analogues suggested that compound **11**, the 5-thiazole analogue of THI, had essentially the same activity versus concentration profile as THI in causing lymphopenia in mice, while the pental **25** showed a slightly higher activity at the same concentration.

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