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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

George R. Jeoffreys
_Undergraduate of Wollongong_

Alison T. Ung
_Undergraduate of Wollongong, alison_ung@uow.edu.au_

Stephen G. Pyne
_Undergraduate of Wollongong, spyne@uow.edu.au_

Brian W. Skelton
_Undergraduate of Western Australia_

Allan H. White
_Undergraduate of Western Australia_

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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

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

George R. Jeoffreys\textsuperscript{a}, Alison T. Ung\textsuperscript{a*}, Stephen G. Pyne\textsuperscript{a*}, Brian. W. Skelton\textsuperscript{b} and Allan H. White\textsuperscript{b}

\textsuperscript{a}Department of Chemistry, University of Wollongong, Wollongong, NSW, 2522, Australia
\textsuperscript{b}Department of Chemistry, University of Western Australia, Nedlands, WA, 6907, Australia

Summary: The synthesis of four of the diastereoisomers of 2-acetyl-5-(1,2,3,4,5,6-hexahydroxyhexyl)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\textsuperscript{1-7} we required the synthesis of some 5-hexahydroxyhexylthiazole analogues, 4, of the known immunosuppressive agent, (1R, 2S, 3R)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI)\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8}

\begin{center}
\begin{tabular}{ll}
\textbf{1} & \textbf{2} \\
\textbf{3} & \textbf{4}
\end{tabular}
\end{center}

**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.\textsuperscript{7} Attempts to condense the known dioxolanone?, 1,2:3,4:5,6-tri-\textit{O}-isopropylidene-\textit{\delta}-gluconolactone 6\textsuperscript{11} with 5-lithio-2-(1,1-dimethoxyethyl)-thiazole\textsuperscript{7} (THF, -78\textdegree{}C to RT) gave no isolatable condensation products and only 2-(1,1-dimethoxyethyl)-thiazole could be recovered. We suspected that deprotonation of 6 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 chloromethylaluminium 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°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 °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
\[
\begin{align*}
\text{5} & \xrightarrow{a} \text{6} \\
\text{11} & \xrightarrow{b} \text{12} \\
\text{12} & \xrightarrow{c} \text{7} \quad \text{8} \\
\text{12} & \xrightarrow{d} \text{9} \quad \text{10} \\
\text{13} & + \text{14} \\
\text{13} & \xrightarrow{e} \text{15} \quad \text{17} \\
\text{14} & \xrightarrow{e} \text{16} \quad \text{18}
\end{align*}
\]
Reduction of 10 with sodium borohydride in methanol at 0 °C afforded an 87 :13 mixture of the 1,2-\textit{syn}- and 1,2-\textit{anti}-products 13 and 14 respectively, that could not be readily separated by column chromatography. Fortunately pure \textit{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.\textsuperscript{10-13} Similar diastereoselectivities were obtained when 12 was treated with L- or K-selectride (THF) at -78 °C. Treatment of a diethyl ether solution of 10 at -78 °C with precooled (-78 °C) DIBAL-H in diethyl ether was highly diastereoselective (dr >98 : <2) and gave essentially pure \textit{anti}-product 14 in 90% yield. While an \textit{anti}-product would be expected for reduction of an \textit{\alpha}-ether substituted ketone under chelation control the OTBS group is normally too hindered to participate in such a mechanism.\textsuperscript{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-\textit{O}-silylated \textit{cis}-1,3-dioxolane 16 with a number of reducing agents (NaBH\textsubscript{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 °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 \(-78^\circ C\) 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 °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 TBSOCH₂ 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. The stereochemistry of 24 and 27 was confirmed by single crystal X-ray analysis (Fig. 7 and 8).

4-Bromo-2-(1,1-dimethoxyethyl)thiazole⁶ underwent trans-metallation at –78 °C and was then treated with the lactone 21 at –78 °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 °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
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 pentahydroxypentyl 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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14. For the reductions of related thiazolyl ketones see: (a) A. Dondoni, D. Perrone, Synthesis 1993, 1162.

