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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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-\(O\)-isopropylidened-erythrono-1,4-lactone or 5-\(O\)-(\textit{tert}-butyl(dimethyl)silyl)-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

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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, (1R, 2S, 3R)-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. Thus THI and its analogues have potential applications as an immunosuppressive agent in organ transplant biology or for preventing the onset of diabetes. 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 pentahydroxypentyl derivative 3 showed a slightly higher activity at the same concentration.

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-erythro-1,4-lactone or D-ribonolactone followed by reductive ring-opening of the resulting lactols to give protected versions of the requisite analogues. Attempts to condense the known dioxolanone?, 1,2:3,4:5,6-tri-O-isopropylidene-6-gluconolactone 6 with 5-lithio-2-(1,1-dimethoxyethyl)-thiazole (THF, -78°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 $\beta$-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
Reduction of 10 with sodium borohydride in methanol at 0 °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 °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 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. 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 (NaBH₄, 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 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 °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)thiazole° 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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References


14. For the reductions of related thiazolyl ketones see: (a) A. Dondoni, D. Perrone, Synthesis 1993, 1162.

