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Asymmetric Synthesis of (1*R*, 2*S*, 3*R*)-2-Acetyl-5-(1,2,3,4-tetrahydroxybutyl)thiazole

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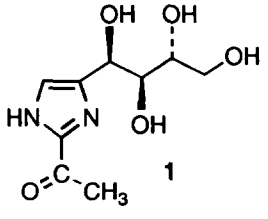
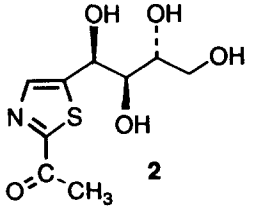
Abstract: A method for preparing the thiazole analogue **2** of the biologically active compound (1*R*, 2*S*, 3*R*)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole **1** is reported.

(1*R*, 2*S*, 3*R*)-2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) **1**, a constituent of Caramel Colour III, has been found to depress blood lymphocyte counts in both mice and rats.[1] THI produces lymphopenia, apparently without toxic effects, in rats and mice and is able to affect the immune competence in the rat in quite small quantities (e.g. 1-50ppm in drinking water).[2] THI has also been reported to prevent spontaneous and cyclophosphamide-induced diabetes in non-obese diabetic mice.[3] To investigate the structure-activity relationships of this structurally simple but biologically intriguing molecule we have developed a general and flexible synthesis of THI and its analogues.[4,5] We now report the asymmetric synthesis of the thiazole analogue **2** of THI as outlined in Schemes 1 and 2.



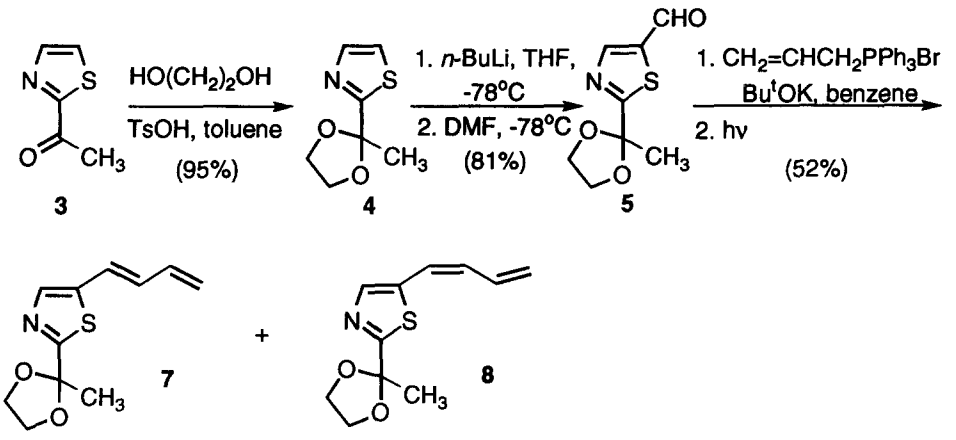
1



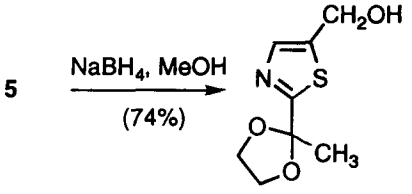
2

Commercially available 2-acetylthiazole **3** was converted to the ketal **4** in 95% yield using standard conditions. Metallation of **4** using *n*-butyl lithium in THF[6,7] at -78°C followed by treatment of the corresponding 5-lithio derivative with DMF at -78°C gave the aldehyde **5** in 81% yield. The regiochemistry of this metallation-formylation step was that expected from previous literature reports[6] and was unequivocally determined by single crystal X-ray structural analysis on the alcohol **6** (Fig. 1, Tables 1-3) that was obtained

Scheme 1



by simple sodium borohydride reduction of **5** (eq. 1). The Wittig reaction between **5** and allyl triphenylphosphonium bromide, under phase transfer catalysis,[8] gave an inseparable 2 : 1 mixture of the (*E*) and (*Z*) dienes, **7** and **8**, respectively. Upon irradiation of a solution of this mixture with UV light the ratio of **7** and **8** changed to 3 : 1. (Scheme 1).



(eq. 1)

Catalytic asymmetric dihydroxylation (AD) of the 3 : 1 mixture of **7** and **8** at 0 °C for 18 h using commercially available AD mix-α,[4,5,9,10] additional chiral ligand ((DHQ)$_2$-PHAL (4 mol %) and methanesulfonamide (2 equiv.) in *tert*-BuOH / H_2O gave a 7 : 1 mixture of the (3*S*)- and (3*R*) diols **9** and **10** plus unreacted **8.** The diols were separated from **8** by column chromatography and then converted to their acetonides derivatives **11** and **12** respectively in 95% yield using 2,2-dimethoxypropane in the presence of boron trifluoride.etherate catalyst. The acetonides derivatives **11** and **12** were readily separated on silica gel. Hydrolysis of **11** with aqueous 10 % hydrochloric acid / acetone (2 : 1) at reflux for 2 h gave pure diol **9** in 64% enantiomeric purity as determined from ^{1}H NMR analysis of its corresponding Mosher diester.

Catalytic asymmetric dihydroxylation (AD) of **11** at 0 °C for 5 days using commercially available AD mix-β,[4,5,9,10] additional chiral ligand ((DHQD)$_2$-PHAL (4 mol %) and methanesulfonamide (2 equiv.) in *tert*-BuOH / H_2O gave the *syn* (1*R*, 2*S*)-diol **13** in 84% yield and moderate diastereoselectivity (d.r. = 87 : 13) as determined by ^{1}H NMR analysis. Diastereomerically pure **13** could be obtained by simple recrytallisation. The relative stereochemistry of **13** was established by single crystal X-ray structural analysis (Fig. 1, Tables 1-3) and the absolute stereochemistry assigned to **13** is based on our previous work[4,5] and Sharpless's mnemonic.[10,11] The enantiomeric purity of **13** was determined to be 78 % from analysis of its Mosher diester.

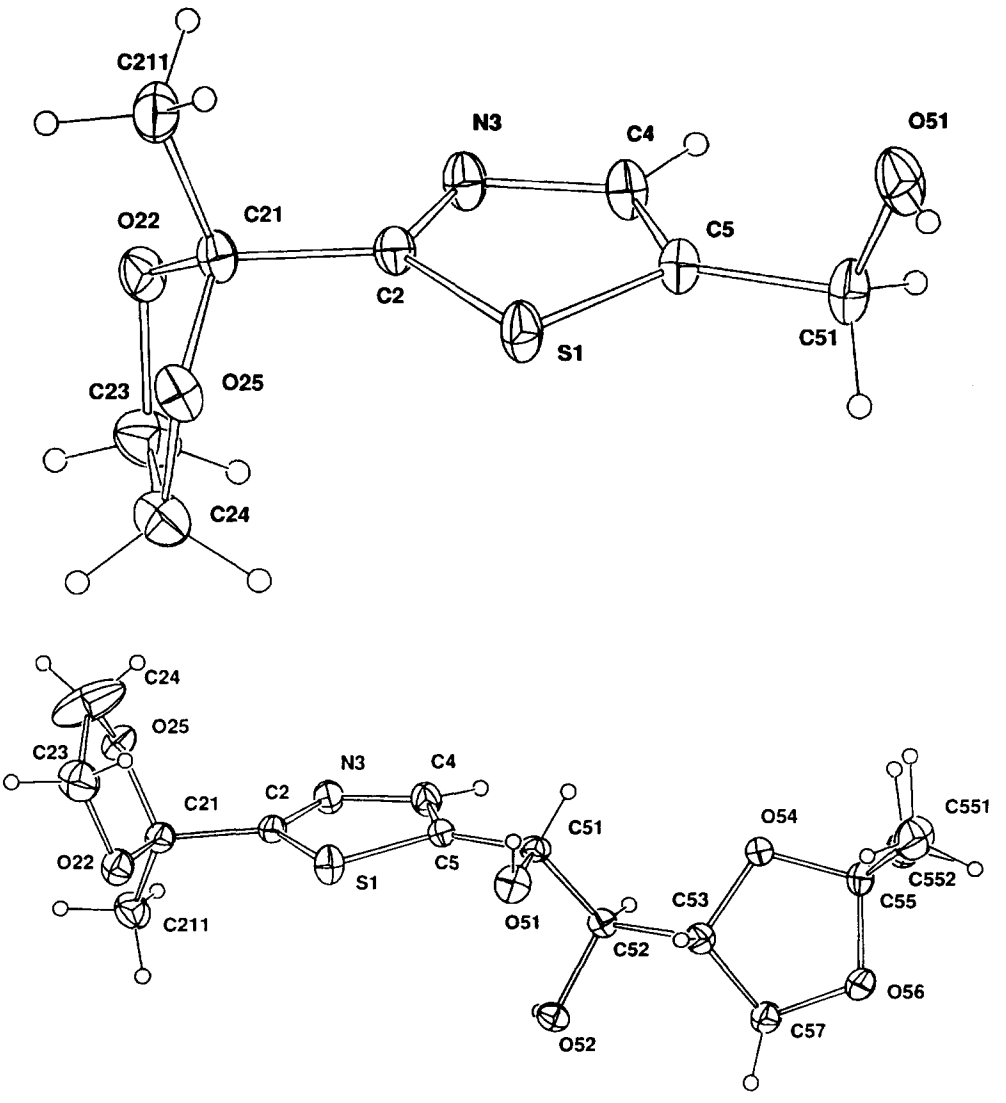


Figure 1. Projection of **6** (top structure) and **13** (bottom structure); 20% thermal ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å. Note that the ellipsoid in **13** for C(24), possibly a foil for unresolved disorder, is suggestive of a pair of alternative ring configurations superimposed.

Finally deprotection of **13** was achieved in two steps by first hydrolysis of the diol protecting group with aqueous hydrochloric acid / acetone at reflux for 2 h and then deprotection of the acetyl group with $PdCl_2(MeCN)_2$ in aqueous acetone[12] to give the desired compound **2** in 87% overall yield.

In summary, we have developed a method for the synthesis of the thiazole analogue of the biologically active molecule THI **1** using a double AD reaction of a 1,3-butadiene.[13] This method should be generally useful for preparing other heterocyclic analogues of THI. The biological properties of **2** are currently under investigation.

Scheme 2

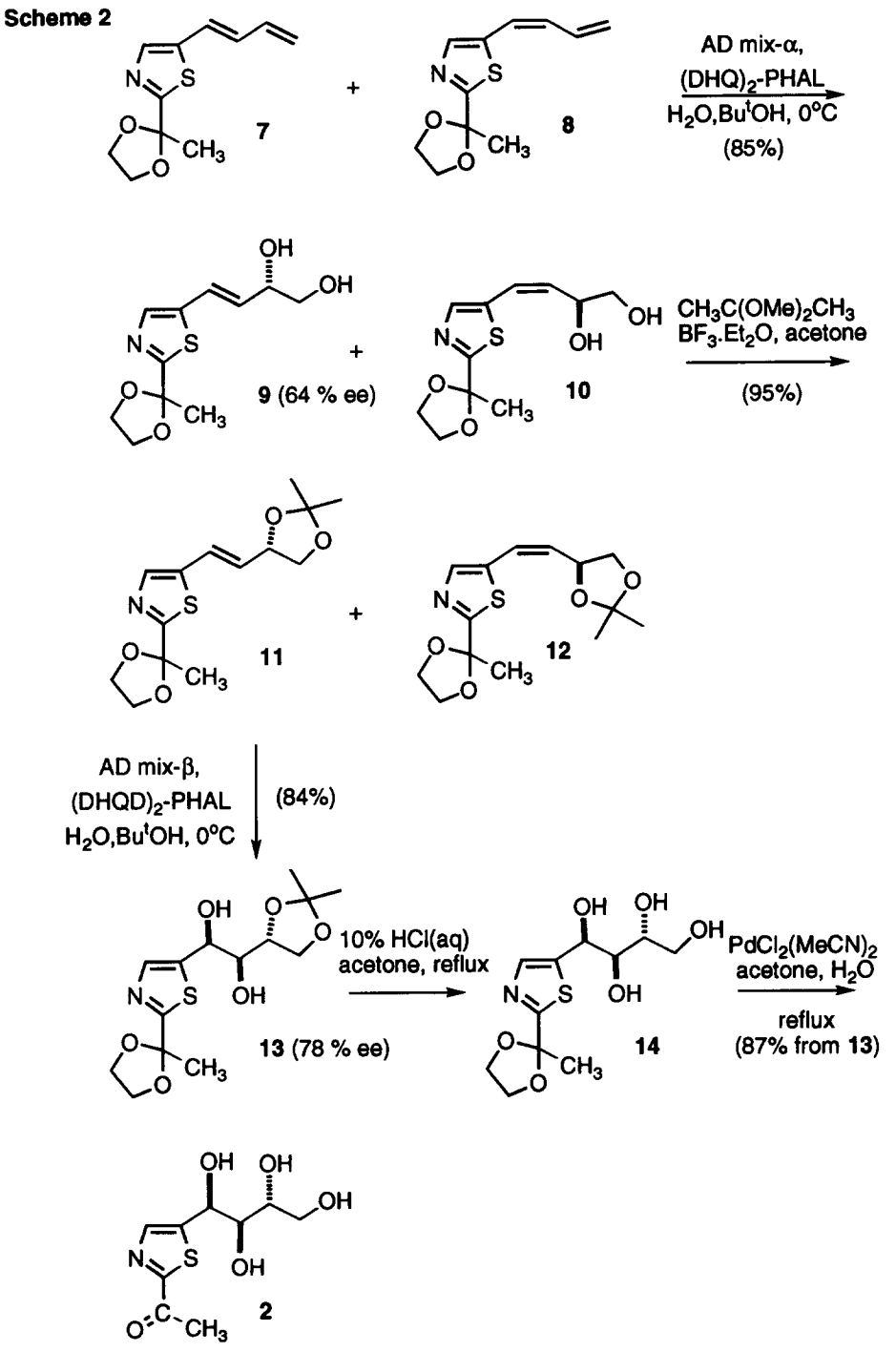

7
8
AD mix-α,
(DHQ)2-PHAL
H2O,BuᵗOH, 0°C
(85%)
9 (64 % ee)
10
CH3C(OMe)2CH3
BF3.Et2O, acetone
(95%)
11
12
AD mix-β,
(DHQD)2-PHAL
H2O,BuᵗOH, 0°C
(84%)
13 (78 % ee)
10% HCl(aq)
acetone, reflux
14
PdCl2(MeCN)2
acetone, H2O
reflux
(87% from 13)
2

Table 1. Summary of Crystallographic Data[a] for **6** and **13**

	6	**13**
molecular formular	$C_8H_{11}NO_3S$	$C_{14}H_{21}NO_6S$
molecular weight	201.3	331.4
crystal system	triclinic	orthorhombic
space group	$P\bar{1}$	$P2_12_12_1$
a, Å	12.386(2)	27.32(1)
b, Å	6.604(1)	9.765(9)
c, Å	6.1882(9)	6.032(2)
α, deg	66.43(1)	
β, deg	85.64(1)	
γ, deg	87.39(1)	
V, Å^3	462.5(1)	1609
Z	2	4
D calc., gcm^{-3}	1.44_5	1.36_8
crystal dimension, mm	0.52x0.45x0.20	0.50x0.42x0.28
F(000)	212	704
μ_{Mo}, cm^{-1}	3.2	0.8
$2\theta_{max}$, deg	55	60
N	2110	2713
N_o	1654	1709
R	0.034	0.055
R_w	0.037	0.053
n_v	163	285

[a]Common to both structures: Unique room temperature diffractometer data sets were measured (monochromatic Mo *K*α radiation, λ = 0.7107_3 Å; 2θ/θ scan mode; *T* ~ 295 K) yielding *N* independent reflections, N_o with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinements without absorption correction (neutral atom complex scattering factors, Xtal 3.2 program system; anisotropic thermal parameter forms for C, N, O, S and $(x, y, z, U_{iso})_H$ being refined.) Conventional *R*, R_w (statistical weights) on |*F*| are quoted. The specimen of **13** was optically active, its absolute configuration being assigned from the chemistry.

Table 2. Bond Lengths (Å)and Bond Angles (deg) for **6**

S(1)-C(2)	1.713 (2)	C(21)-O(25)	1.416 (3)
S(1)-C(5)	1.720 (2)	O(22)-C(23)	1.420 (4)
C(2)-C(21)	1.522 (2)	C(23)-C(24)	1.501 (3)
C(2)-N(3)	1.300 (2)	C(24)-O(25)	1.435 (3)
C(21)-C(211)	1.504 (4)	N(3) -C(4)	1.381 (2)
C(21)-O(22)	1.413 (2)	C(4)-C(5)	1.346 (2)
C(5)-C(51)	1.502 (3)	C(51)-O(51)	1.414 (3)

C(2)-S(1)-C(5)	89.95(8)	O(22)-C(23)-C(24)	105.8(2)
S(1)-C(2)-C(21)	121.1 (1)	C(23)-C(24)-O(25)	104.8(2)
S(1)-C(2)-N(3)	114.7 (1)	C(21)-O(25)-C(24)	106.3(1)
C(2)-C(21)-C(211)	112.1(2)	C(2)-N(3)-C(4)	110.0(1)
C(2)-C(21)-O(22)	109.6(1)	N(3)-C(4)-C(5)	116.5(2)
C(2)-C(21)-O(25)	109.1(1)	S(1)-C(5)-C(4)	108.8(1)
C(211)-C(21)-O(22)	110.2(1)	S(1)-C(5)-C(51)	123.2(1)
C(211)-C(21)-O(25)	109.7(2)	C(4)-C(5)-C(51)	127.9(2)
O(22)-C(21)-O(25)	105.9(2)	C(5)-C(51)-O(51)	112.0(2)
C(21)-O(22)-C(23)	105.5(1)	C(21)-C(2)-N(3)	124.2 (1)

Table 3. Bond Lengths (Å) and Bond Angles (deg) for **13**

S(1)-C(2)	1.707(5)	C(5)-C(51)	1.492(7)
S(1)-C(5)	1.717(4)	C(51)-O(51)	1.427(6)
C(2)-C(21)	1.523(6)	C(51)-C(52)	1.524(7)
C(2)-N(3)	1.299(6)	C(52)-O(52)	1.432(6)
C(21)-C(211)	1.500(9)	C(52)-C(53)	1.513(7)
C(21)-O(22)	1.412(6)	C(53)-O(54)	1.434(6)
C(21)-O(25)	1.420(6)	C(53)-C(57)	1.485(7)
O(22)-C(23)	1.417(9)	O(54)-C(55)	1.431(6)
C(23)-C(24)	1.430(1)	C(55)-C(551)	1.480(1)
C(24)-O(25)	1.360(1)	C(55)-C(552)	1.491(9)
N(3) -C(4)	1.389(7)	C(55)-O(56)	1.435(7)
C(4)-C(5)	1.339(7)	O(56)-C(57)	1.427(7)
C(2)-S(1)-C(5)	89.6(2)	C(5)-C(51)-C(52)	112.0(4)
S(1)-C(2)-C(21)	121.3(3)	O(51)-C(51)-C(52)	108.0(4)
S(1)-C(2)-N(3)	115.5(3)	C(51)-C(52)-O(52)	109.6(4)
C(2)-C(21)-C(211)	111.4(4)	C(51)-C(52)-C(53)	113.1(4)
C(21)-C(2)-N(3)	123.2(4)	O(52)-C(52)-C(53)	107.3(4)
C(2)-C(21)-O(22)	109.6(4)	C(52)-C(53)-O(54)	107.7(4)
C(2)-C(21)-O(25)	109.6(4)	C(52)-C(53)-C(57)	116.6(4)
C(211)-C(21)-O(22)	109.5(5)	O(54)-C(53)-C(57)	102.8(4)
C(211)-C(21)-O(25)	110.2(4)	C-(53)-O(54)-C(55)	108.5(4)
O(22)-C(21)-O(25)	106.4(4)	C(21)-O(22)-C(23)	107.8(5)
O(22)-C(23)-C(24)	104.6(7)	O(54)-C(55)-C(551)	110.4(5)
C(23)-C(24)-O(25)	110.4(9)	O(54)-C(55)-C(552)	108.8(5)
C(21)-O(25)-C(24)	105.8(6)	O(54)-C(55)-O(56)	105.7(4)
C(2)-N(3)-C(4)	109.2(4)	C(551)-C(55)-C(552)	113.0(6)
N(3)-C(4)-C(5)	116.5(4)	C(551)-C(55)-O(56)	108.4(5)

S(1)-C(5)-C(4)	109.2(3)	C(552)-C(55)-O(56)	110.3(5)
S(1)-C(5)-C(51)	119.9(3)	C(55)-O(56)-C(57)	106.3(4)
C(4)-C(5)-C(51)	130.9(4)	C(53)-C(57)-O(56)	102.7(4)
C(5)-C(51)-O(51)	110.1(4)		

Experimental

General procedures were as described previously.[4] X-ray data has been submitted to the Cambridge Crystal Data Centre, University Chemical Lab., Lensfield Rd., Cambridge, CB2 1EW, UK.

***2-(2-Methyl-1,3-dioxolanyl)thiazole* 4**

A mixture of 2-acetylthiazole (6.40 g, 0.05 mol), ethylene glycol (4.00 g, 0.065 mol) and *p*-toluene sulfonic acid (0.32 g) was dissolved in toluene (120 mL) in a round bottom flask fitted with Dean-Stark trap and a condenser. The resulting mixture was refluxed for 18 h or until close to the theoretical amount of water (2 mL) has been collected in the trap. The reaction mixture was cooled to RT, extracted excessively with a 10% aqueous solution of NaOH (100 mL x 5) then water (100 mL x 3) and dried over K_2CO_3. The solvent was removed to give a yellow oil as crude product which was purified by column chromatography (20% ethyl acetate/hexane) to give **4** as a pale yellow oil (8.19 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, 1H, J = 3.3 Hz, H4), 7.29 (d, 1H, J = 3.3 Hz, H5), 4.14-4.00 (m, 4H, (CH_2)$_2$), 1.84 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 77.5 MHz) δ 172.07 (C2), 143.00 (C4), 119.18 (C5), 106.72 (OCO), 85.00 ((CH_2)$_2$), 25.01(CH_3). MS (ES +ve) *m/z* 171.9 (M+1, 100%).

***2-(2-Methyl-1,3-dioxolanyl)thiazole-5-carboxaldehyde* 5**

n-BuLi (0.63 mmol) was added to a solution of thiazole **4** (0.158 g, 0.916 mmol) in dry THF (2 mL) at -78 °C under a N_2 atmosphere. After 20 min., a solution of DMF (0.11 mL) in dry THF (0.8 mL) was added dropwise into the mixture at -78 °C. The reaction mixture was allowed to stir at the same temperature for 20 min. and at RT for 2 h. Saturated NH_4Cl solution (2 mL) was then added and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with a satd. aqueous solution of NaCl (10 mL) and dried over $MgSO_4$. The solvent was removed to give a yellow oil which was purified by column chromatography (30% ethyl acetate/ hexane) to give **5** as a colourless oil (0.15 g, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.00 (s, 1H, HCO), 8.36 (s, 1H, H5), 4.14- 3.98 (m, 4H, (CH_2)$_2$), 1.80 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75.7 MHz) δ 182.45(HCO), 180.50 (C2), 151.84 (C4), 139.79 (C5), 106.84 (OCO), 65.62 ((CH_2)$_2$), 24.94 (CH_3).

***2-(2-Methyl-1,3-dioxolanyl)-5-(hydroxymethyl)thiazole* 6**

A solution of $NaBH_4$ (0.02 g) in 0.1M NaOH (0.4 mL) was added to a stirred solution of the thiazole-5-carboxaldehyde **2** (0.251 g, 1.26 mmol) in MeOH (20 mL) at 0 °C. The reaction mixture was left to stir at 0 °C for 1 h and at RT for another hour. The solvent was removed and the residue was taken up in CH_2Cl_2 (20 mL). The organic solution was washed with a satd. aqueous solution of NaCl (20 mL) and dried over $MgSO_4$. The solvent was removed to give thick oil which solidified upon standing at 0 °C. The crude solid was recrystallised from toluene to give needle-like crystals (0.19 g, 74%), m.p: 66-67 °C. ^{1}H NMR ($CDCl_3$, 300

MHz) δ 7.56 (s, 1H, H4), 4.82 (d, 2H, J = 5.4 Hz, $C\underline{H}_2OH$), 4.11-3.97 (m, 4H, $(C\underline{H}_2)_2$), 2.92 (t, 1H, $CH_2O\underline{H}$), 1.79 (s, 3H, $C\underline{H}_3$). MS (ES +ve) *m/z* 202.1 (M+1, 70%), 116 (57%), 87 (100%). Anal. Cal. for $C_8H_{11}O_3NS$; C, 47.75; N, 6.96; H, 5.51; found C, 47.65; N, 6.86; H, 5.55.

(1*E*,)- and (1*Z*)-*2-(2-methyl-1,3-dioxolanyl)-5-(1,3-butadienyl)thiazole* 7 and 8

To a stirred mixture of the thiazole-5-carboxaldehyde **5** (0.856 g, 4.32 mmol), allyl triphenylphosphonium bromide (2.10 g, 4.44 mmol), triethylbenzylammonium chloride (0.017 g) and hydroquinone (0.024 g) in dry benzene (40 mL) at RT was added potassium *tert*-butoxide (0.68 g, 6.07 mmol) in one portion and the mixture was stirred at 80 °C for 30 min. Petroleum spirit (40 mL) was then added and the mixture was left to stir for 10 min. The mixture was filtered through a column of silica gel under suction and the column was further eluted with 30% ethyl acetate/hexane (250 mL). The solvent was removed to give a dark yellow oil which was purified by column chromatography (30% ethyl acetate/hexane) to give a pale yellow oil which consisted of a mixture of *cis* and *trans* isomers in the ratio of 1:2. This mixture was dissolved in $CHCl_3$ (50 mL) and the resulting solution was irradiated with a 150 W medium pressure mercury lamp under a N_2 atmosphere for 3 h. The solvent was removed to give a dark yellow oil which consisted of *cis* and *trans* isomers in the ratio of 1:3. The product (0.488 g, 51%) was used for the next experiment without further purification. **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H, H4), 6.64 (d, 1H, J = 14.7 Hz, thia-C$\underline{H}$=CH), 6.56 (d, 1H, J = 9.6 Hz, thia-CH=C$\underline{H}$), 6.45 (t, 1H, J = 13.8 Hz, C$\underline{H}$=CH_2), 5.33 (dd, 1H, J = 1.5, 16.5 Hz, CH=C$\underline{H}$aHb), 5.21 (dd, 1H, J = 1.5, 9.9 Hz, CH=CHaHb), 4.13-4.00 (m, 4H, $(C\underline{H}_2)_2$), 1.82 (s, 3H, $C\underline{H}_3$). **8:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (s, 1H, H4), 6.97 (dddd, 1H, J = 0.6, 10.1, 11.6, 16.5 Hz, thia-CH=C$\underline{H}$), 6.41 (d, 1H, J = 9.9 Hz, thia-C$\underline{H}$=CH), 6.22 (t, 1H, J = 11.4, C$\underline{H}$=CH_2), 5.45 (ddd, 1H, J = 0.6, 0.9, 16.4 Hz, CH=C$\underline{H}$aHb), 5.35 (ddd, 1H, J = 0.6, 0.9, 9.3, CH=CHa$\underline{H}$b), 4.13-4.00 (m, 4H, $(C\underline{H}_2)_2$), 1.83 (s, 3H, CH_3).

(1*E*, 3*R*)- and (1*Z*, 3*S*)-*2-(2-Methyl-1,3-dioxolanyl)-5-(3,4-dihydroxy-1-butenyl)thiazole* 9 and 10

A mixture of AD mix-α (4.69 g), $MeSO_2NH_2$ (0.63 g) and $(DHQ)_2$-PHAL (0.106 g) was added to a cold solution of the dienes **7** and **8** (0.758 g, 3.39 mmol) in *tert*-butanol/ H_2O (16 mL, 1:1). The reaction mixture was left to stir at 0°C for 18 h. Solid Na_2SO_3 (5.16 g) was then added to the reaction mixture at 0°C and the mixture was allowed to warm up to RT over 1 h. The mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with a satd. aqueous solution of NaCl (50 mL) and dried over $MgSO_4$. The solvent was removed to give a yellow oil which was transferred to the top of a small column of silica gel (2 - 3 g). The column was first eluted with 20% ethyl acetate/hexane to removed the unreacted *cis*-diene **8**, then with ethanol (200 mL) to remove the product from the column. Ethanol was removed to give a pale yellow oil (0.419 g, 85%) which consisted of the *trans* and *cis* diols, **9** and **10**, in the ratio of 7:1.

9: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.62 (s, 1H, H4), 6.84 (ddd, 1H, J = 0.6, 1.8, 15.8 Hz, thia-C$\underline{H}$=CH), 6.61 (dd, 1H, J = 5.7, 15.6 Hz, thia-CH=CH), 4.28 (m, 1H, CHOH), 4.11-3.99 (m, 4H, $(CH_2)_2$), 3.59-3.46 (m, 2H, CHaHb), 1.72 (s, 3H, CH_3). ^{13}C NMR (acetone-d_6, 77.5 MHz) d 170.71 (C2); 140.81 (C4); 137.37 (C5), 131.64 (thia-$\underline{C}$H=CH), 120.54 (thia-CH=$\underline{C}$H), 106.48 ($\underline{C}CH_3$), 72.00 (H$\underline{C}$OH), 65.76 ($\underline{C}$HaHb), 65.01 (($\underline{C}H_2)_2$), 24.78 ($\underline{C}H_3$).

***(1E , 3R)- and (1Z , 3S)-2-(2-Methyl-1,3-dioxolanyl)-5-[3,4-O-(2'-propylidine)-3,4-dihydroxybut-1-enyl]thiazole* 11 and 12**

A mixture of *trans* and *cis* diols **9** and **10** (0.194 g, 0.76 mmol) was dissolved in dry acetone (3 mL) and 2,2-dimethoxypropane (0.85 mL) was added. $BF_3.Et_2O$ (0.006 mL) was added to the reaction mixture which was left to stir at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (10 mL). The organic layer was washed with a half satd. aqueous solution $NaHCO_3$ (10 mL), satd. aqueous solution NaCl (10 mL) and dried over $MgSO_4$. The solvent was removed to give a dark yellow oil (0.215, 95%) which was purified on a TLC plate (40% ethyl acetate/hexane).

11: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (s, 1H, H4), 6.72 (d, 1H, J = 15.6 Hz, thia-CH=CH), 5.95 (dd, 1H, J = 7.2, 15.6 Hz, thia-CH=CH), 4.59 (ddd, 1H, J = 0.9, 6.8, 14.2 Hz, HCO), 4.12 (dd, 1H, J = 8.4, 6.3 Hz, CHaHb), 4.09-3.96(m, 4H, $(CH_2)_2$), 3.63 (dd, 1H, J = 8.1, 7.5 Hz, CHaHb), 1.77 (s, 3H, $OCCH_3$), 1.42 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.28 (C2), 141.91 (HC4), 137.09 (C5), 129.96 (thia-CH=CH), 122.96 (thia-CH=CH), 109.60 (CH_3CCH_3), 106.89 ($OCCH_3$), 76.41 (CHO), 69.28 (CHaHb), 65.37 ($(CH_2)_2$), 26.59 ($OCCH_3$), 25.78 (CH_3CCH_3), 25.08 (CH_3CCH_3). $[\alpha]_D^{22}$: +26.43 (c = 0.21, $CHCl_3$). HRMS: cal for $C_{14}H_{22}O_4NS$, 298.11134; found 298.11128.

12: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (s, 1H, H4), 6.64 (dd, 1H, J = 0.6, 1.2, 11.4 Hz, thia-CH=CH), 5.73 (dd, 1H, J = 8.4, 11.4 Hz, thia-CH=CH), 5.08 (ddd, 1H, J = 1.2, 7.5, 16.1 Hz, HCO), 4.32 (dd, 1H, J = 6.2, 8.1 Hz, CHaHb), 3.65 (dd, 1H, J = 7.5, 8.1 Hz, CHaHb); 1.83 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 77.5 MHz) δ 172.79 (C2), 144.01 (HC4), 133.86 (C5), 130.35 (thia-CH=CH), 121.92 (thia-CH=CH); 109.73 (CH_3CCH_3), 106.98 ($OCCH_3$), 72.72 (HCO), 69.14 (CHaHb); 65.45 ($(CH_2)_2$), 26.70 ($OCCH_3$), 25.81 (CH_3); 25.19 (CH_3). $[\alpha]_D^{25}$: -2.39 (c = 0.39, $CHCl_3$)

***(1R, 2S, 3R)-2-(2-Methyl-1,3-dioxolanyl)-5-[3,4-O-(2'-propylidine)-3,4-dihydroxybutyl] thiazole* 13**

A mixture of AD mix-β (0.34 g), $MeSO_2NH_2$ (0.046 g) and $(DHQD)_2$-PHAL (8 mg) was added to a cold solution of *trans*-protected diol **11** (63 mg, 0.24 mmol) in *tert*-butanol/ H_2O (2.4 mL, 1:1). The reaction mixture was left to stir at 0°C for 5 days. Solid Na_2SO_3 (0.43 g) was then added to the mixture at 0°C and the mixture was allowed to warm up to RT over 1 h. The mixture was diluted with H_2O (3 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic extracts were dried over $MgSO_4$ and the CH_2Cl_2 was removed to give pale yellow oil which upon standing at 0°C formed crystalline solid. The solid was recrystallised from toluene to give needle-like crystals (0.058 g, 84%). ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.65 (s, 1H, H4), 5.13 (s, 1H, HCOH(1R)), 4.21 (m, 1H, HCOH(2S)), 4.10-3.93 (m, 4H, $(CH_2)_2$), 3.58 (d, 1H, J = 7.5 Hz, HCO(3R)), 3.03 (d, 2H, J = 7.5 Hz, CHaHb), 1.72 (s, 3H, $OCCH_3$), 1.35 (s, 3H, CH_3CCH_3), 1.29 (s, 3H, CH_3CCH_3). ^{13}C NMR (acetone-d_6, 77.5 MHz) δ 171.67 (C2), 141.84 (C5), 139.81 (HC4), 108.68 (CCH_3), 106.73 (CH_3CCH_3), (CHOH(1R)), 75.42 (HCOH(2S)), 67.08 (HCO(3R)), 66.54 (CHaHb), 65.08 ($(CH_2)_2$), 26.27 ($OCCH_3$), 26.28 (CH_3CCH_3), 24.25 (CH_3CCH_3). $[\alpha]_D^{18}$: +5.11(c = 0.43, $CHCl_3$). HRMS: cal. for $C_{14}H_{20}O_6NS$, 332.11675; found 332.11814.

***(1R, 2S, 3R)-2-Acetyl-5-(1,2,3,4-tetrahydroxybutyl)thiazole* 2**

The protected-tetraol **13** (0.21 g, 0.64 mmol) was dissolved in acetone/water (14 mL, 1:1) and conc. HCl (6.2 mL). The resulting solution was left to reflux for 2 h. The solvent was removed to give a dark brown oil. The oil was dissolved in water (20 mL) and the resulting solution was washed with ether (20 mL x 3) by extraction. The water was removed under reduced pressure to give a dark brown oil which was dissolved in

wet acetone (20 mL). To this solution was added $PdCl_2(CH_3CN)_2$ (0.1 equiv., 0.064 mmol, 0.016 g) and the mixture was refluxed overnight. The solvent was removed and the residue was taken up in water (30 mL). The aqueous solution was washed with ether (30 mL x 3). The water was removed to give dark brown oil which was purified by column chromatography (30% methanol/ethyl acetate) to give compound **8** as bright yellow solid (0.136 g, 87%). ^1H NMR (D_2O, 300 MHz) δ 7.85 (s, 1H, H4), 5.28 (s, NH, HCOH(1R)), 3.74-3.65 (m, 2H, HCOH(2S) and HCOH(3R)), 3.56-3.49 (m, 2H, CHaHb), 2.55 (s, 3H, $OCCH_3$). ^{13}C NMR (D_2O, 77.5 MHz) δ 193.77 (C=O), 165.57 (C2), 148.93 (C5), 141.00 (C4); 73. 41(HCOH(1R)), 70.54 (HCOH(2S)), 66.33 (HCOH(3R)), 62.37 (CHaHb), 25.28 ($OCCH_3$). $[\alpha]_D^{23}$: +7.68 (c = 0.34, H_2O). HRMS: cal. for $C_9H_{14}O_5NS$, 248.05925; found 248.05896.

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