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Asymmetric synthesis of (1*R*,2*S*,3*R*)-2-acetyl-4-(1,2,3,4-tetrahydroxybutyl)thiazole

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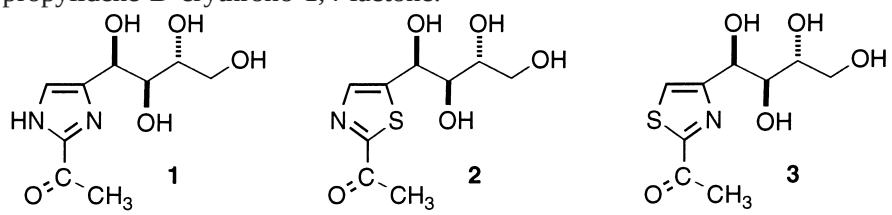
Abstract

Two different methods for preparing the thiazole analogue **3** of the biologically active compound (1*R*,2*S*,3*R*)-2-acetyl-4(5)-(1,2,3,4- tetrahydroxybutyl)imidazole **1** are reported.

1. Introduction

(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. 1–50 ppm 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,[4–6] including the 5-thiazole analogue **2**.[7] We now report the asymmetric synthesis of the 4-thiazole analogue **3** of THI, using two different synthetic strategies. The first strategy involved a double Sharpless asymmetric dihydroxylation (AD) of a 1,3-butadiene to introduce the tetrahydroxybutyl side chain of **3**. In an alternative synthesis of **3** the tetrahydroxybutyl side chain was introduced via the condensation of a 4-lithiothiazole derivative and 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone.



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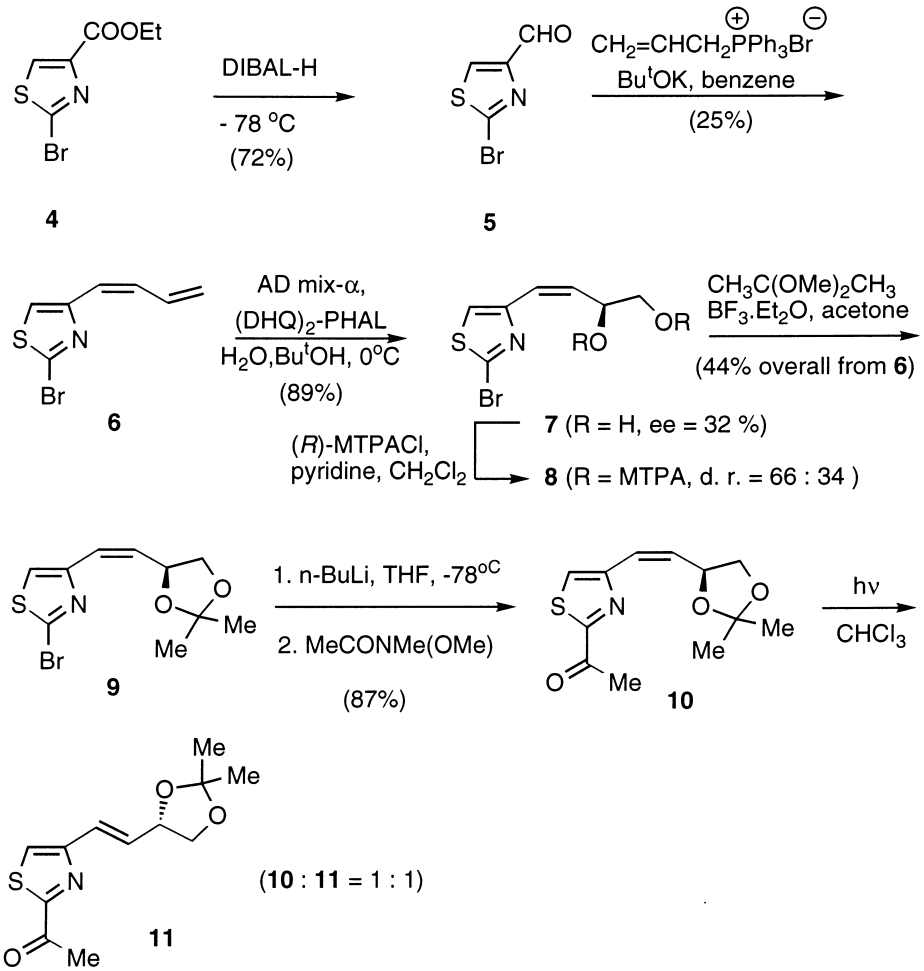
2. Results and discussion

2.1. Synthesis of 3 via double Sharpless asymmetric dihydroxylation (AD)

Ethyl 2-bromothiazole-4-carboxylate **4**[8a,b] was reduced with DIBAL to its carboxaldehyde derivative **5** in 72% yield using standard conditions (Scheme 1). The Wittig reaction between **5** and allyl triphenylphosphonium bromide, under phase transfer catalysis,[9] gave exclusively the (*Z*)-diene **6**, however the yield of **6** was poor (25%). Catalytic asymmetric dihydroxylation (AD) of **6** at 0°C for 18 h using commercially available AD mix-α,[4,5,10,11] additional chiral ligand [$(DHQ)_2$-PHAL (4 mol%)] and methanesulfonamide (2 equiv.) in *tert*-BuOH/H_2O gave the diol **7** in 89% crude yield.

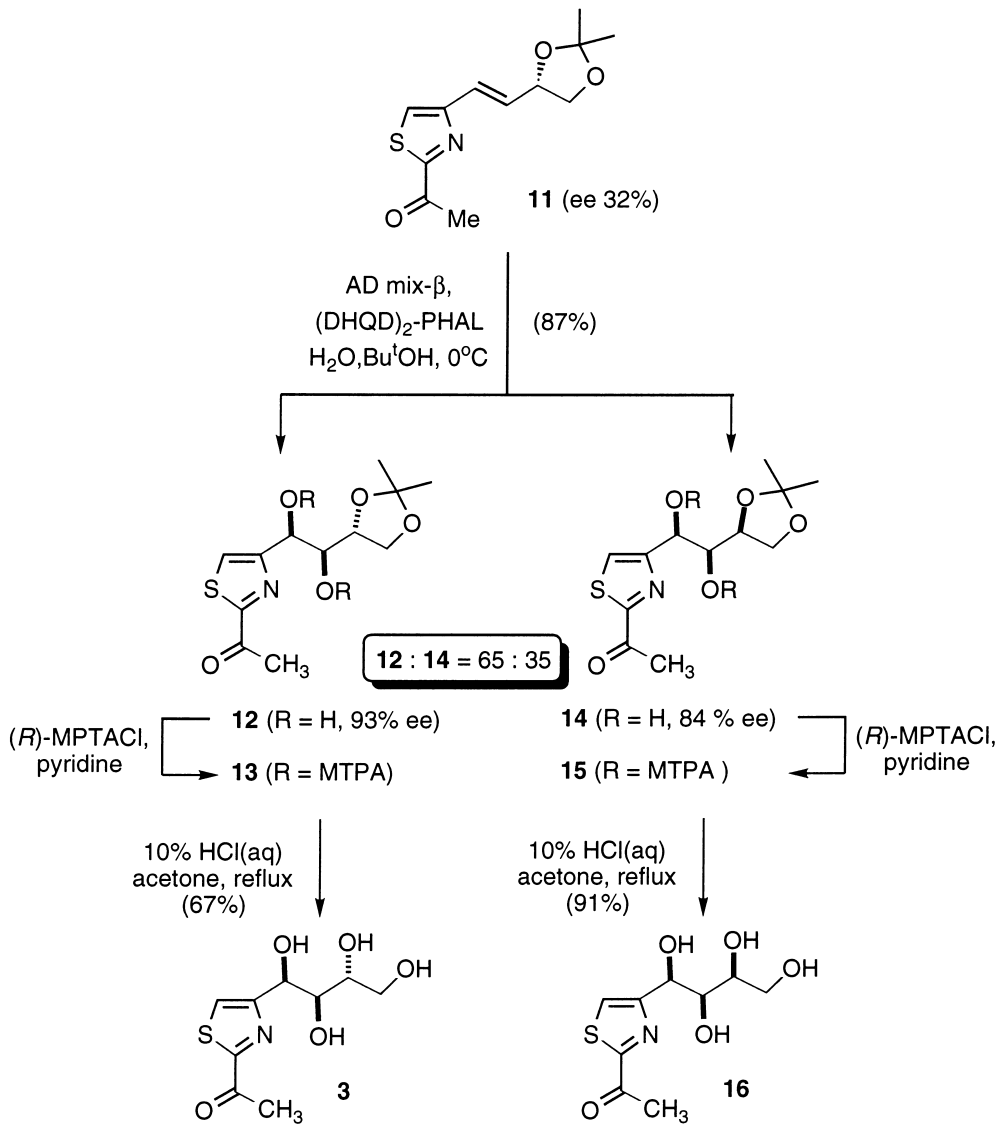


Scheme 1.

The enantiomeric excess of **7** was determined to be 32% from ^{1}H NMR analysis of its Mosher diester **8** which was obtained as a 66:34 mixture of diastereoisomers. The (*S*) stereochemistry assigned to **7** was based upon Sharpless's mnemonic (compare with Scheme 3).[11–13] Diol **7** was converted to its acetonide derivative **9**, using 2,2-dimethoxypropane in the presence of $BF_3 \cdot Et_2O$, in 44% overall yield from **6** after purification by column chromatography. Lithium–bromine exchange between **9** and *n*-butyllithium gave the corresponding 2-lithiothiazole derivative that was acetylated with *N*-methoxy-*N*-methylacetamide[4,6]

to give the 2-acetylthiazole **10** in 87% yield. Irradiation of a solution of **10** in chloroform with UV light (140 W mercury lamp) under nitrogen for 2.5 h gave an equilibrium mixture (1:1) of the (*E*) and (*Z*) alkenes **11** and **10** that could be separated by PTLC (Scheme 1). Recovered **10** could be further recycled by photolysis to produce more **11**.

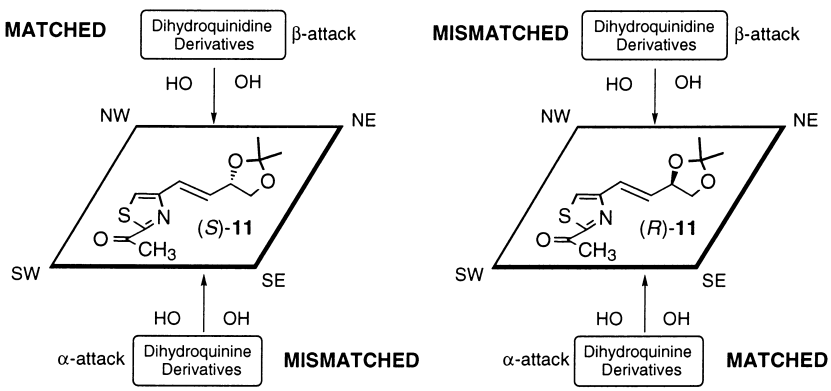
Catalytic asymmetric dihydroxylation (AD) of **11** at 0°C for 5 days using commercially available AD mix-β,[4,5,9,10] additional chiral ligand [$(DHQD)_2$-PHAL (4 mol%)] and methanesulfonamide (2 equiv.) in *tert*-BuOH/H_2O gave a mixture of the *syn* diols **12** and **14** in a ratio of 65:35, respectively (Scheme 2). These diastereoisomeric diols were readily separated by column chromatography on silica gel. The enantiomeric excess of the individual diols, **12** and **14**, was determined to be 93% and 84%, respectively, from ^{1}H NMR analysis of their respective Mosher diesters **13** and **15**.



Scheme 2.

The AD reaction of both (*S*)-**11** and (*R*)-**11** therefore proceeds with very high π-facial diastereo-

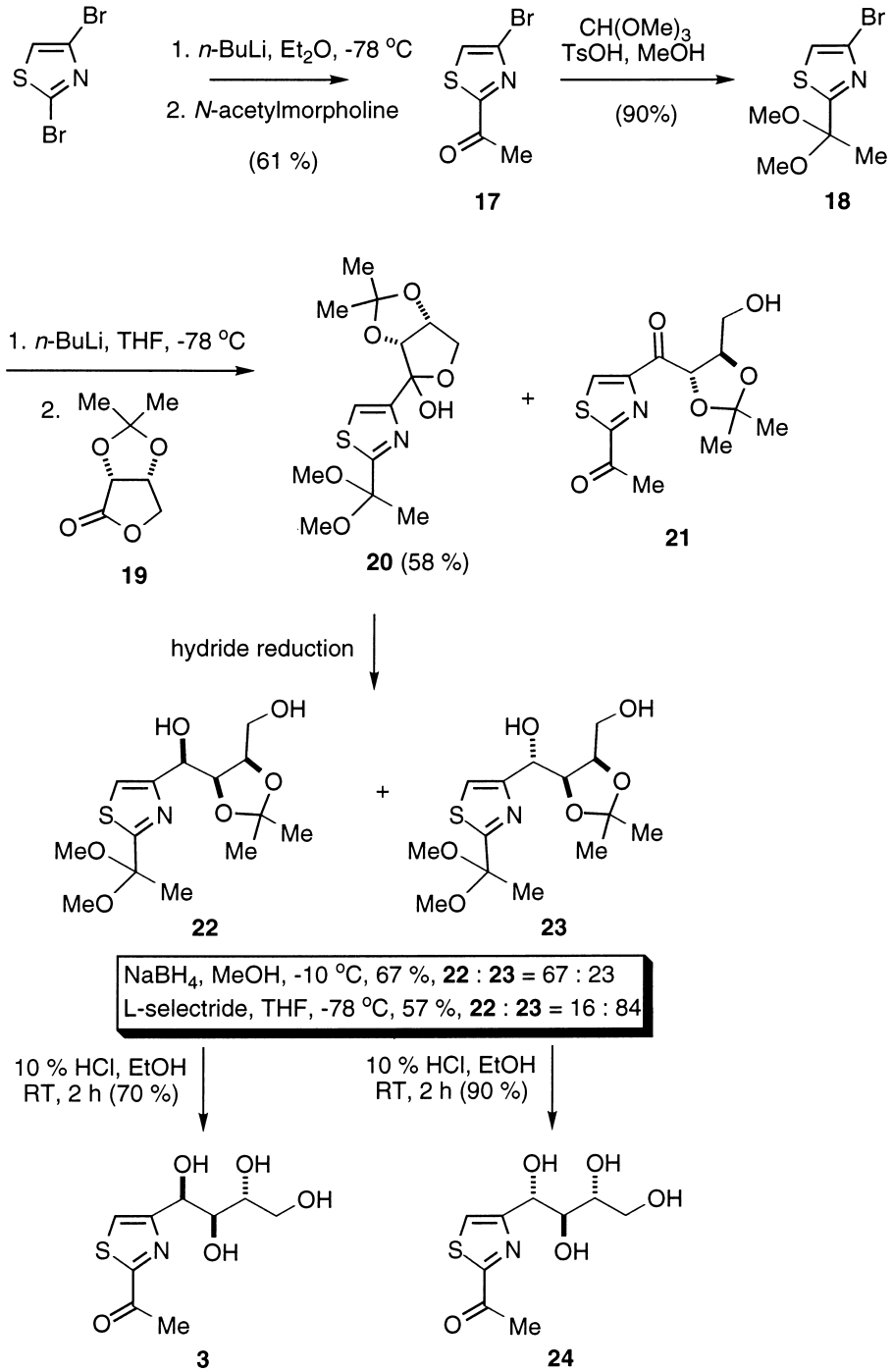
selectivity and thus allows for the preparation of **12** and **14**, respectively, in high enantiomeric purities. We have found that the AD reaction of chiral *trans*-disubstituted alkenes related to **11** were also highly diastereoselective, in both the matched (d.r.=99:1) and mismatched cases (d.r.=95:5).[6] The stereochemistry assigned to **12** and **14** was based on our previous work[4–6] and Sharpless's mnemonic (Scheme 3).[10,11] The AD reaction of (*S*)-**11** (Scheme 3) would be expected to be the matched case while that of (*R*)-**11** would be the mismatched case. These predictions are consistent with the magnitude of the enantiomeric purities of their respective AD products **12** and **14**. Finally, deprotection of **12** and **14** was achieved by acid hydrolysis with aqueous hydrochloric acid/acetone at rt for 2 h to give the desired compound **3** and its diastereoisomer **16**, respectively. The ^{1}H NMR spectrum of **3** [δ (D_2O) 5.00 (d, J=2.4 Hz, H1′)] was similar to that of THI **1** [δ (D_2O) 4.91 (s, H1′)], while the ^{1}H NMR of **16** was very different [δ (D_2O) 4.89 (d, J=5.7 Hz, H1′)]. The latter spectrum more closely matched that of the (1′*R*,2′*S*,3′*S*) analogue of THI **1** [δ (D_2O) 5.04 (d, J=4.8 Hz, H1′)].[6]



Scheme 3.

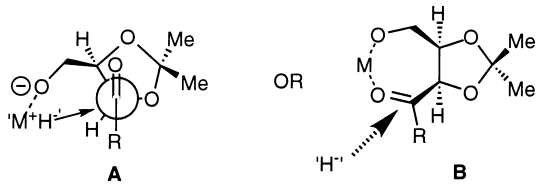
2.2. *Synthesis of* ***3*** *from 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone*

Treatment of 2,4-dibromothiazole[14] with *n*-BuLi in THF at −78°C followed by acetylation of the resulting 2-lithiothiazole compound with *N*-acetylmorpholine[15] gave 2-acetyl-4-bromothiazole **17** in 61% yield (Scheme 4). The keto group of **17** was protected as its dimethoxyketal **18** and its 4-lithiothiazole derivative was treated with 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone **19** at −78°C to give the lactol **20** in 58% yield along with a small amount (<10%) of the C-2 epimerized ketone **21**. Treatment of **20** with sodium borohydride/methanol at −10°C gave a 67:33 mixture of the diastereoisomeric diols **22** and **23**, respectively, which could readily separated by PTLC. The stereochemistry assigned to **22** and **23** was determined by ^{1}H NMR analysis whereby comparisons were made with their 5-thiazole analogues of known stereochemistry[16] while that of **23** was unequivocally determined from a single-crystal X-ray structural analysis.[17] The stereochemistry of the major diol **22** is that expected from the Felkin–Anh transition state model **A**[18] or the γ-chelated transition state structure **B**[19] in which hydride attack would be expected to occur from the convex face of the bicyclo[5.3.0]decane ring system in **B**. In contrast, the reduction of the lactol **20** with L-selectride in THF at −78°C proceeded with reverse diastereoselectivity and gave a 16:84 mixture of the diastereoisomeric diols **22** and **23**, respectively. Acid hydrolysis of the individual diastereoisomers **22** and **23** gave **3** and **24**, respectively. Compound **3** had identical spectral properties to those obtained for **3** prepared according to Scheme 2 above.



Scheme 4.

In summary, we have developed two independent methods for the synthesis of the 4-thiazole analogue **3** of the biologically active molecule THI **1** either using a double AD reaction of a 1,3-butadiene[13] or from 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone.



A Felkin-Anh transition state model with complexation of M^+H^- to the primary alkoxide

B γ-chelation model with attack of H^- from the convex face of the bicyclo[5.3.0]decane

3. Experimental

General procedures were as described previously.[4] All NMR were determined in $CDCl_3$ solution, unless otherwise indicated, at 300 MHz (^{1}H NMR) or 77.5 MHz (^{13}C NMR).

*3.1. Ethyl 2-bromothiazole-4-carboxylate **4***

The title compound was prepared in two steps using the following modifications to the literature procedures. A mixture of solid thiourea (7.95 g, 0.104 mol) and ethyl bromopyruvate (20.40 g, 0.104 mol) was cautiously heated with stirring at 100°C for 1 h. After cooling, the dark solid that formed was washed with acetone and filtered to give a dark yellow solid which was further purified by crystallisation from ethanol to give ethyl 2-aminothiazole-4-carboxylate hydrobromide salt as a colourless solid (22.92 g, 87%), m.p: 184–185°C (lit.[8a] m.p: 179–180°C). ^{1}H NMR (D_2O) δ 7.56 (s, 1H, H5), 4.23 (q, 2H, J=6.9 Hz, C$\underline{H}_2$), 1.20 (t, 3H, J=6.9 Hz, C$\underline{H}_3$). ^{13}C NMR (D_2O) δ 178.93 (C$\underline{O}$), 167.34 (C2), 139.94 (C4), 126.40 (C$\underline{5}$), 72.28 (C$\underline{H}_2$), 22.14 (C$\underline{H}_3$). MS (ES +ve) *m/z* 173.00 (M+1, 100%), 127.00 (100%). A solution of dry $CuBr_2$ (10.72 g, 48 mmol) and *tert*-butyl nitrite (6.20 g, 60 mmol) in dry acetonitrile (160 mL) was cooled to 0°C.[8b] Then solid ethyl 2-aminothiazole-4-carboxylate (10.12 g, 40 mmol) was added portion-wise to the solution with stirring over 20 min. The reaction mixture was allowed to warm to rt over 2 h, then was poured into a 20% solution of HCl (450 mL) and the aqueous solution was extracted with ether (800 mL). The combined ether extracts were washed with a 10% solution of HCl and dried over $MgSO_4$. The solvent was removed to give a dark orange oil which solidified upon standing at rt. The crude product was purified by column chromatography (15% ethyl acetate/hexane) to give **4** as a white crystalline solid (6.59 g, 88%), m.p: 65–65.5°C (lit.[8a] m.p: 68.5–69.2°C) and ethyl 2,5-dibromothiazole-4-carboxylate as a pale yellow oil (1.83 g). **4**: ^{1}H NMR δ 8.11 (s, 1H, H5), 4.41 (q, 2H, J=6.9 Hz, C$\underline{H}_2$), 1.38 (t, 3H, J=6.9 Hz, C$\underline{H}_3$). ^{13}C NMR δ 159.98 (C$\underline{O}$), 147.21 (C2), 136.63 (C4), 130.69 (C5), 61.53 (C$\underline{H}_2$), 14.17 (C$\underline{H}_3$). MS (ES +ve) *m/z* 236.9 (M+1, 90%), 235.9 (M, 100%).

Ethyl 2,5-dibromothiazole-4-carboxylate: ^{1}H NMR δ 4.40 (q, 2H, J=7.2 Hz, C$\underline{H}_2$), 1.39 (t, 3H, J=7.2 Hz, C$\underline{H}_3$). ^{13}C NMR δ 159.55 (C$\underline{O}$), 143.73 (C2), 135.62 (C4), 118.76 (C5), 61.97 (CH_2), 14.13 (C$\underline{H}_3$).

*3.2. 2-Bromothiazole-4-carboxaldehyde **5***

To a solution of **4** (3.00 g, 12.7 mmol) in dry THF/CH_2Cl_2 (1:1, 200 mL) at −78°C was added dropwise a solution of DIBAL (3 equiv., 38 mmol, 25.4 mL of 1 M solution) to maintain the temperature at −70°C. The reaction was left to stir at −78°C for 5 h then was quenched with dry methanol (20 mL) at the same temperature. The reaction mixture was poured into an ice-cold solution of 1 M HCl (100 mL) and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined extracts were washed with

a sat. solution of NaCl and dried over $MgSO_4$. The solvent was removed to give a white solid material which was purified by column chromatography (25% ethyl acetate/hexane) to give **5** as a white solid (1.751 g, 72%), m.p: 122–123°C, plus a trace of its over-reduced alcohol derivative. ^{1}H NMR δ 9.94 (s, 1H, CHO), 8.12 (s, 1H, H5). ^{13}C NMR δ 183.19 (CHO), 154.33 (C2), 137.68 (C4), 130.29 (C5). MS (ES +ve) *m/z*: 193.4 (M+1, 90%), 191.50 (M−1, 100%).

*3.3. (Z)-2-Bromo-4-(1,3-butadienyl)thiazole **6***

A mixture of the aldehyde **5** (1.134 g, 5.91 mmol), allyltriphenylphosphonium bromide (2.3 g, 6.07 mmol), triethylbenzylammonium chloride (0.023 g) in dry benzene (50 mL) was set to stir at 0°C. Potassium *tert*-butoxide (0.93 g, 8.3 mmol) was added in small portions to the reaction mixture. After stirring for 30 min at rt, the mixture was diluted with petroleum spirit (50 mL) and filtered through a small column of silica gel and the column was washed with 10% ethyl acetate/hexane (100 mL). The solvent was removed to give a yellow oil which was purified by column chromatography to give a colourless oil (0.33 g, 25%). The product was relatively unstable and was directly used for the next reaction. ^{1}H NMR δ 7.6 (m, 1H, thia–CH=CH), 7.07 (s, 1H, H5), 6.53–6.4 (m, 1H, thia–CH=CH), 6.26–6.20 (m, 1H, CH=CHaHb), 5.40 (dd, 1H, J=2.1, 16.8 Hz, CHaHb), 5.32 (dd, 1H, J=1.8, 10.3 Hz, CHaHb).

*3.4. (1Z,3S)-2-Bromo-4-(3,4-dihydroxy-1-butenyl)thiazole **7***

A mixture of AD mix-α[10] (2.12 g), $(DHQ)_2$-PHAL (0.005 g), $MeSO_2NH_2$ (0.28 g) was added to a cold solution of the diene **8** (0.33 g, 1.53 mmol) in *tert*-butanol/H_2O (1:1, 15 mL). The reaction mixture was left to stir at 0°C for 20 h. Solid Na_2SO_3 (1.28 g) was then added to the mixture at 0°C and allowed to warm up to rt over 1 h. The mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with a sat. solution of NaCl and dried over $MgSO_4$. The solvent was removed to give a dark yellow oil (0.34 g, 89%). ^{1}H NMR δ 7.09 (s, 1H, H5), 6.39 (ddd, 1H, J=0.6, 1.5, 11.1 Hz, thia–CH=CH), 5.82 (dd, 1H, J=6.3, 11.7 Hz, thia–CH=CH), 4.84 (m, 1H, HCOH), 3.76 (dd, 1H, J=3.6, 11.1 Hz, CHaHb), 3.66 (dd, 1H, J=7.5, 11.1 Hz, CHaHb). ^{13}C NMR δ 152.40 (C2), 151.07 (C4), 132.84 (C5), 123.39 (thia–CH=CH), 119.73 (thia–CH=CH), 68.54 (HCOH), 66.02 (CH_2). MS (ES +ve) *m/z*: 251.5 (M+1, 55%). HRMS calcd for $C_7H_9BrNO_2S$ 249.95377; found 249.95374.

*3.5. Mosher diester **8***

A mixture of the diol **7** (0.048 g, 0.192 mmol), (*R*)-(−) MTPA-Cl (0.150 g, 0.563 mmol), and a crystal of *N*,*N*-dimethylaminopyridine was dissolved in CH_2Cl_2 (4 mL). Pyridine (7 drops) was added to the solution and it was left to stir at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and was washed with a cold solution of 5% HCl then a cold solution of $NaHCO_3$, and dried over $MgSO_4$. The diastereoisomeric ratio (66:34) was determined by ^{1}H NMR on the crude reaction mixture. The solvent was removed to give a dark yellow oil which was purified by thin layer chromatography (30% ethyl acetate/hexane) to give a yellow oil (55 mg, 44%, d.r.=66:34). Major diastereoisomer: ^{1}H NMR δ 7.54–7.31 (m, 10H, 2×C_6H_5), 7.20 (s, 1H, H5), 6.93–6.86 (m, 1H, thia–CH=CH), 6.42 (dd, 1H, J=1.5, 12.0 Hz, thia–CH=CH), 5.41 (dd, 1H, J=7.5, 11.7 Hz, HCO), 4.86 (dd, 1H, J=2.7, 12.0 Hz, CHaHb), 4.43 (dd, 1H, J=6.9, 12.0 Hz, CHaHb), 3.43 (bs, 3H, OCH_3), 3.40 (d, 3H, J=0.9 Hz, OCH_3). MS (ES +ve) *m/z* 682 ($M(Br^{81})$+1, 80%), 682.1 ($M(Br^{80})$+1, 50%). Minor diastereoisomer: ^{1}H NMR δ 7.54–7.31 (m, 10H, C_6H_5), 7.19 (s, 1H, H5), 7.02–6.96 (m, 1H, thia–CH=CH), 6.43 (dd, 1H, J=1.2, 12.0 Hz, thia–CH=CH),

5.61 (dd, 1H, J=7.8, 11.7 Hz, HCO), 4.81 (dd, 1H, J=2.7, 12.0 Hz, CHaHb), 4.45 (dd, 1H, J=6.0, 12.0 Hz, CHaHb), 3.52 (d, 3H, J=0.9 Hz, OCH_3), 3.49 (d, 3H, J: 0.9 Hz, OCH_3).

3.6. (1Z,3S)-2-Bromo-4-[3′,4-′O-(2-propylidene)-3′,4′-dihydroxy-but-1-enyl]thiazole **9**

2,2-Dimethoxypropane (1.11 mL) was added to a solution of diol **7** (0.611 g, 22.45 mmol) in dry acetone (10 mL) then $BF_3 \cdot Et_2O$ (18 μL) was added dropwise and the mixture was left to stir at rt under N_2 atmosphere for 4 h. The acetone was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (60 mL). The resulting solution was washed with a half sat. solution of $NaHCO_3$, a sat. solution of NaCl and dried over $MgSO_4$. The solvent was removed to give a dark oil which was purified by column chromatography (20% ethyl acetate/hexane) to give **9** as a pale yellow oil (0.576 g, 81%). ^{1}H NMR δ 7.11 (s, 1H, H5), 6.39 (dd, 1H, J=1.5, 12.0 Hz, thia–CH=CH), 5.84 (dd, 1H, J=7.5, 11.7 Hz, thia–CH=CH), 5.55 (dddd, 1H, J=1.5, 7.8, 7.8, 7.8 Hz, HCO), 4.47 (dd, 1H, J=6.3, 8.1 Hz, CHaHb), 3.65 (dd, 1H, J=6.9, 8.1 Hz, CHaHb), 1.47 (s, 3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR δ 152.27 (C2), 135.39 (C4), 133.00 (C5), 122.42 (thia–CH=CH), 121.02 (thia–CH=CH), 109.15 ($C(CH_3)_2$), 73.19 (HCO), 69.62 (CH_2), 26.62 (CH_3), 25.65 (CH_3). MS (ES +ve) *m/z*: 292.38 ($M(Br^{81})$+1, 60%), 291.50 ($M(Br^{80})$+1, 50%).

3.7. (1Z,3S)-2-Acetyl-4-[3′,4′-O-(2-propylidene)-3,4-dihydroxy-1-but-1-enyl]thiazole ***10***

n-Butyl lithium (2.25 mmol) was added to a solution of protected diol **9** (0.438 g, 1.5 mmol) in dry ether (20 mL) at −78°C and the resulting solution was left to stir at this temperature for 90 min. A solution of freshly distilled *N*-methoxy-*N*-methylacetamide (0.5 g, 4.85 mmol) in dry ether (5 mL) was then added dropwise and the reaction mixture was left to stir at −78°C for 2 h then warmed to rt over 2 h. The reaction mixture was diluted with ether (20 mL) and the resulting solution was washed with a sat. solution of $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed to give a yellow oil which was purified by column chromatography (20% ethyl acetate/hexane) to give the title compound as a pale yellow oil (0.33 g, 87%). ^{1}H NMR δ 7.49 (s, 1H, H5), 6.51 (dd, 1H, J=1.5, 11.7 Hz, thia–CH=CH), 5.92 (dd, 1H, J=7.5, 11.7 Hz, thia–CH=CH), 5.67 (dddd, 1H, J=1.5, 6.6, 7.2, 7.8 Hz, HCO), 4.40 (dd, 1H, J=6.3, 8.1 Hz, CHaHb), 3.70 (dd, 1H, J=7.2, 7.8 Hz, CHaHb), 2.72 (s, 3H, $COCH_3$), 1.48 (s, 3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR δ 191.34 (CO), 166.45 (C2), 154.28 (C4), 133.54 (C5), 124.87 (thia–CH=CH), 122.88 (thia–CH=CH), 109.42 ($C(CH_3)_2$), 73.53 (HCO), 69.71 (CH_2), 26.69 ($COCH_3$), 25.95 (CH_3), 25.71 (CH_3). MS (ES +ve) *m/z*: 254.03 (M+1, 100%).

3.8. (1E,3S)-2-Acetyl-4-[3,4-O-(2′-propylidene)-3,4-dihydroxybut-1-enyl]thiazole ***11***

The *cis*-alkene **10** (0.33 g, 1.303 mmol) was dissolved in $CHCl_3$ (100 mL) and the resulting solution was first purged with N_2 for 10 min and then irradiated with a 140 W mercury lamp under N_2 for 3 h. The solvent was removed to give a dark yellow oil which was a 1:1 mixture of **10** and **11**. These geometric isomers could be separated by thin layer chromatography (20% ethyl acetate/hexane) to give the *E* and *Z* isomers **10** and **11**. ^{1}H NMR δ 7.41 (s, 1H, H5), 6.74 (d, 1H, J=15.6 Hz, thia–CH=CH), 6.63 (dd, 1H, J=6.3, 15.6 Hz, thia–CH=CH), 4.71 (ddd, 1H, J=6.6, 7.05, 7.5 Hz, HCO), 4.20 (dd, 1H. J=6.3, 8.1 Hz, CHaHb), 3.73 (dd, 1H, J=7.8, 7.8 Hz, CHaHb), 2.72 (s, 3H, $COCH_3$), 1.49 (s, 3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR δ 191.77 (CO), 166.93 (C2), 155.01 (C4), 139.22 (C5), 124.80 (thia–CH=CH), 122.26 (thia–CH=CH), 76.34 (HCO), 69.46 (CH_2), 26.64 ($COCH_3$), 25.95 (CH_3), 25.85 (CH_3).

3.9. (1R,2S,3R)- and (1R,2S,3S)-2-Acetyl-4-[3,4-O-(2′-propylidene)-3,4-dihydroxybutyl]thiazole **12** and **14**

A mixture of AD mix-β (0.78 g), $(DHQD)_2$-PHAL (0.017 g) $MeSO_2NH_2$ (0.103 g) and 5 mol% of $K_2OsO_4 \cdot 2H_2O$ was added to a cold solution of *trans*-protected diol **11** (0.136 g, 0.53 mmol) in *tert*-butanol/H_2O (1:1, 8 mL) at 0°C. The resulting mixture was left to stir at 0°C for 5 days then Na_2SO_3 (0.93 g) was added at 0°C and the mixture was allowed to warm up to rt over 1 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (4×30 mL). The combined organic extracts were washed with a sat. solution of NaCl and dried over $MgSO_4$. The solvent was removed to give a yellow oil (0.123 g, 87%, d.r.=65:35) which was purified by thin layer chromatography (75% ethyl acetate/hexane) to afford **12** (32% yield) and **14** (32% yield). **12**: ^{1}H NMR δ 7.70 (d, 1H, J=0.9 Hz, H5), 5.05 (ddd, 1H, J=0.6, 2.4, 7.5 Hz, H1′), 4.18–4.11 (m, 2H, 2×OH), 4.05 (ddd, 1H, J=2.4, 2.7, 3.0 Hz, H2′), 3.99 (ddd, 1H, J=2.4, 6.6, 6.45 Hz, H3′), 3.35 (d, 1H, J=7.8 Hz, C<u>Ha</u>Hb), 3.26 (d, 1H, J=6.0 Hz, CHa<u>Hb</u>), 2.68 (s, 3H, COC<u>H</u>$_3$), 1.45 (s, 3H, C<u>H</u>$_3$), 1.35 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR δ 191.20 (<u>C</u>O), 1167.10 (C2), 159.18 (C4), 123.12 (C5), 109.58 (<u>C</u>(CH$_3$)$_2$), 75.34 (C1′), 73.98 (C2′), 69.14 (C3′), 66.80 (<u>C</u>H$_2$), 26.73 (CO<u>C</u>H$_3$), 25.92 (<u>C</u>H$_3$), 25.17 (<u>C</u>H$_3$). $[\alpha]_D^{20}$ −14.0 (c 0.5, CH_2Cl_2). Anal. calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87; S, 11.16; found C, 50.23; H, 5.99; N, 4.79; S, 11.17. **14**: ^{1}H NMR δ 7.70 (d, 1H, J=0.9 Hz, H5), 5.00 (ddd, 1H, J=0.9, 3.3, 3.0 Hz, H1′), 4.36 (ddd, 1H, J=3.6, 6.9, 6.6 Hz, H2′), 4.12–3.98 (m, 3H, H3′ and 2×OH), 3.46 (d, 1H, J=3.9 Hz, C<u>Ha</u>Hb), 2.77 (d, 1H, J=7.8 Hz, CHa<u>Hb</u>), 2.68 (s, 3H, COC<u>H</u>$_3$), 1.48 (s, 3H, C<u>H</u>$_3$), 1,40 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR δ 191.40 (<u>C</u>O), 166.84 (C2), 158.32 (C4), 123.04 (C5), 109.89 (<u>C</u>(CH$_3$)$_2$), 77.06 (C1′), 72.31 (C2′), 72.21 (C3′), 65.95 (<u>C</u>H$_2$), 26.28 (CO<u>C</u>H$_3$), 25.92 (<u>C</u>H$_3$), 25.29 (<u>C</u>H$_3$). $[\alpha]_D^{21}$ −22.7 (c 0.75, CH_2Cl_2). MS (ES +ve) *m/z*: 288.4 (M+1, 45%), 287.6 (M, 60%). HRMS calcd for $C_{12}H_{18}NO_2S$ 288.09054; found 288.09057.

3.10. Mosher diesters **13** and **16**

These diesters were prepared from the diols **12** and **14**, respectively, as described above for the synthesis of **8**. Compound **13** was a 96.5:3.5 mixture of diastereoisomers, while **14** was a 92:8 mixture of diastereoisomers. **13**: ^{1}H NMR (major diastereoisomer) δ 7.56–7.26 (m, 10H, 2×C$_6$<u>H</u>$_5$), 7.16 (d, 1H, J=0.9 Hz, H5), 6.56 (dd, 1H, J=0.6, 1.8 Hz, H1′), 5.63 (dd, 1H, J=1.8, 8.4 Hz, H2′), 4.08 (ddd, 1H, J=5.0, 5.7, 8.4 Hz, H3′), 3.86 (dd, 1H, J=5.7, 8.7 Hz, C<u>Ha</u>Hb), 3.75 (dd, 1H, J=5.7, 8.7 Hz, CHa<u>Hb</u>), 3.53 (d, 3H, J=0.9 Hz, OC<u>H</u>$_3$), 3.33 (d, 3H, J=0.9 Hz, OC<u>H</u>$_3$), 2.50 (s, 3H, COC<u>H</u>$_3$), 1.50 (s, 3H, C<u>H</u>$_3$), 1.33 (s, 3H, C<u>H</u>$_3$). MS (ES +ve) *m/z*: 720.2 (M+1, 35%). **16**: ^{1}H NMR (major diastereoisomer) δ 7.51–7.29 (m, 10H, 2×C$_6$<u>H</u>$_5$), 7.03 (s, 1H, H5), 6.27 (d, 1H, J=2.4 Hz, H1′), 5.67 (dd, 1H, J: 2.7, 7.5 Hz, H2′), 4.13 (ddd, 1H, J=6.3, 7.2, 13.5 Hz, H3′), 4.05 (dd, 1H, J=7.7, 7.7 Hz, C<u>Ha</u>Hb), 3.92 (dd, 1H, J=5.7, 9.0 Hz, CHa<u>Hb</u>), 3.49 (s, 3H, OC<u>H</u>$_3$), 3.37 (s, 3H, OC<u>H</u>$_3$), 2.64 (s, 3H, COC<u>H</u>$_3$), 1.38 (s, 3H, C<u>H</u>$_3$), 1.29 (s, 3H, C<u>H</u>$_3$). Minor diastereoisomer: δ 6.97 (s, 1H, H5), 6.33 (d, J=7.2 Hz, H1′). MS (ES +ve) *m/z*: 720.0 (M+1, 100%).

3.11. (1R,2S,3R)-2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)thiazole **3**

Compound **12** (57 mg, 0.198 mmol) was dissolved in acetone/H_2O (1:1, 4 mL) and conc. HCl (1.71 mL) was added to the solution. The reaction mixture was left to stir at rt for 3 h. The acetone was removed under reduced pressure at 25°C and water was removed on a freeze-dryer to give a yellow solid (33 mg, 67%) that was judged to be >95% pure by ^{1}H NMR. ^{1}H NMR (D_2O/DCl) δ 7.80 (s, 1H, H5), 5.00 (d, 1H, J=2.4 Hz, H1′), 3.74 (dd, 1H, J=2.4, 7.8 Hz, H2′), 3.66–3.52 (m, 2H, H3′ and C<u>Ha</u>Hb), 3.45 (dd, 1H,

J=5.4, 11.1 Hz, CHaHb), 2.49 (s, 3H, CH_3). ^{13}C NMR (D_2O/DCl) δ 193.03 (CO), 165.20 (C2), 157.88 (C4), 123.94 (C5), 72.50 (C1′), 70.40 (C2′), 69.95 (C3′), 62.11 (CH_2), 25.28 (CH_3). MS (ES +ve) *m/z*: 248.3 (M+1, 100%), 247.5 (M, 80%). HRMS calcd for $C_9H_{14}NO_5S$ 248.05925; found 248.05927.

3.12. (1R,2S,3S)-2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)thiazole **16**

Compound **14** (10 mg, 0.035 mmol) was dissolved in acetone/H_2O (1:1, 1 mL) and conc. HCl (0.3 mL). The resulting solution was left to stir at rt for 2 h. The acetone was removed under pressure and water was removed on a freeze-dryer to yield a yellow oil (9 mg, 91%) that was judged to be >95% pure by ^{1}H NMR. ^{1}H NMR (D_2O) δ 7.76 (s, 1H, H5), 4.89 (d, 1H, J=5.7 Hz, H1′), 3.83 (dd, 1H, J=3.6, 5.7 Hz, H2′), 3.45 (m, 3H, H3′ and CH_2), 2.53 (s, 3H, CH_3). ^{13}C NMR (D_2O) δ 193.75 (CO), 166.00 (C2), 157.88 (C4), 123.94 (C5), 72.50 (C1′), 70.40 (C2′), 68.43 (C3′), 62.15 (CH_2), 25.29 (CH_3). MS (ES +ve) *m/z*: 248.0 (M+1, 10%), 247.4 (M, 15%). MS (ES −ve) m/z: 282.2 (M+ Cl^-, 15%). $[\alpha]_D^{23}$ −16.0 (c 0.5, H_2O).

3.13. 2-Acetyl-4-bromothiazole **17**

Solid 2,4-dibromothiazole (4.93 g, 20.32 mmol) was dissolved in anhydrous ether (50 mL) and the resulting solution was allowed to stir under N_2 atmosphere at −78°C. To the solution was added *n*-BuLi (1.1 equiv., 22.35 mmol, 14 mL of 1.6 M solution) and the stirring continued for 30 min. To the reaction was then added dropwise 4-acetylmorpholine (1.3 equiv., 26.42 mmol, 3 mL). After stirring for 90 min, the reaction mixture was diluted with ether and the resulting organic layer was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$. The solvent was removed to give a dark yellow solid which was purified by column chromatography to give a white crystalline solid (2.78 g, 66%). ^{1}H NMR δ 7.57 (s, 1H, H5), 2.70 (s, 3H, CH_3); ^{13}C NMR δ 190.36 (CO), 166.91 (C2), 126.92 (C4), 124.96 (C5), 25.80 (CH_3); MS (ES +ve) *m/z* 207.8 (MBr^{81}+1, 20%), 205.8 (MBr^{80}+1, 15%), 205.1 (MBr^{79}+1, 100%); mp 90–91°C. Anal. calcd for C_5H_4BrNOS: C, 29.14; H, 1.96; N, 6.79; S, 15.56. Found: C, 29.25; H, 1.89; N, 6.94; S, 15.29.

3.14. 2-(2,2-Dimethoxyethyl)-4-bromothiazole **18**

To the solution of 2-acetyl-4-bromothiazole **17** (0.85 g, 4.12 mmol) in dry MeOH (15 ml) was added trimethyl orthoformate (41 mmol, 4.84 ml) and *p*-toluene sulfonic acid (0.7 g). After heating under reflux for 24 h and cooling to rt, the reaction mixture was diluted with a saturated solution of $NaHCO_3$ (30 ml). The aqueous layer was extracted with ether and the combined organic extracts were washed with a solution of 1 M NaOH, a saturated solution of NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a brown solid which was purified by column chromatography (10% ethyl acetate/hexane) to give a pale yellow solid (0.94 g, 90%). ^{1}H NMR δ 7.22 (s, 1H, H5), 3.24 (s, 6H, 2×OCH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR δ 172.60 (C2), 124.68 (C4), 118.13 (C5), 100.28 ($C(OCH_3)_2$), 49.21 (2×OCH_3), 23.75 (CH_3); MS (ES +ve) *m/z* 253.9 (MBr^{81}+1, 50%), 251.9 (MBr^{79}+1, 40%), 221.8 ($MBr^{81}-OCH_3$, 100%), 219.9 ($MBr^{79}-OCH_3$, 100%); mp 49–50°C. Anal. calcd for $C_7H_{10}BrNO_2S$: C, 33.35; H, 4.00; N, 5.56; S, 12.72. Found: C, 33.27; H, 3.93; N, 5.13; S, 12.62.

3.15. 2,3-O-Isopropylidene-1-[2-(2,2-dimethoxyethyl)-4-thiazolyl]-α-D-furanose **20**

To a solution of 2-(2,2-dimethoxyethyl)-4-bromothiazole (2.73 g, 10.82 mmol) in anhydrous ether (40 ml) at −78°C was added dropwise *n*-BuLi (11.90 mmol, 7.5 mL of 1.6 M solution). The resulting mixture was left to stir at −78°C for 30 min then a solution of 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone **19** (1.8 g, 11.36 mmol) in anhydrous ether (50 mL) was added. After stirring for 1.5 h, the reaction mixture was diluted with ether and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed to give a dark yellow oil which was purified by column chromatography (75% ethyl acetate/*n*-hexane) to give a mixture of diastereomeric compounds in the ratio of 80:20 (2.06 g, 58%) and plus a small trace of the open-chain ketone.

Major isomer: ^{1}H NMR δ 7.55 (s, 1H, H5), 5.02 (dd, 1H, J=4.2, 6.0 Hz, H2′), 4.69 (d, 1H, J=5.4 Hz, H3′), 4.53 (s, 1H, OH), 4.19 (dd, 1H, J=3.9, 10.2 Hz, CHaHb), 4.05 (d, 1H, J=10.2 Hz, CHaHb), 3.24 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 1,73 (s, 3H, CH_3), 1.50 (s, 3H CH_3CCH_3), 1.32 (CH_3CCH_3); ^{13}C NMR δ 170.49 (C2), 153.17 (C4), 118.76 (C5), 112.50 (C1′), 103.41 (CH_3CCH_3), 100.76 ($C(OCH_3)_2$), 85.58 (C2′), 80.63 (C3′), 71.12 (C4′), 49.32 (OCH_3), 49.29 (OCH_3), 26.24 (CH_3), 24.87 (CH_3CCH_3), 24.01 (CH_3CCH_3); MS (ES +ve) *m/z* 332.0 (M+1, 100%), 300.0 (M−OCH_3, 100%). HRMS calcd for $C_{14}H_{22}NO_6S$ 332.116752; found 332.116785. Minor isomer: ^{1}H NMR δ 7.54 (s, 1H, H5), 4.97 (dd, 1H, J=3.9, 6.3 Hz, H2′), 4.92 (d, 1H, J=6.0 Hz, H3′), 4.50 (s, 1H, OH), 4.12 (dd, 1H, J=7.5, 14.4 Hz, CHaHb), 3.96 (dd, J=3.9, 10.8 Hz, CHaHb), 3.22 (s, 6H, 2×OCH_3), 1.71 (s, 3H, CH_3), 1.62 (s, 3H, CH_3CCH_3), 1.42 (s, 3H, CH_3CCH_3); ^{13}C NMR δ 171.99 (C2), 115.80 (C4), 117.09 (C5), 113.33 (C1′), 101.80 (CH_3CCH_3), 100.71 ($C(OCH_3)_2$), 82.01 (C2′). 80.58 (C3′), 69.77 (C4′), 49.31 (OCH_3), 49.27 (OCH_3), 26.16 (CH_3), 24.87 (CH_3CCH_3), 23.96 (CH_3CCH_3).

3.16. (1R,2S,3R) and (1S,2S,3R)-2-(2,2-Dimethoxyethyl)-4-[2,3-O-(2′-propylidene)-1,4-dihydroxybutyl]thiazole **22** and **23**

To a stirred solution of 4-lactol **20** (0.557 g, 1.68 mmol) in dry MeOH (20 mL) at −10°C was added portionwise solid $NaBH_4$ (10 equiv., 16.80 mmol, 0.67 g). After stirring for 2 h, methanol was removed under reduced pressure, the residue was taken up in H_2O (20 mL) and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a colourless oil which was purified by column chromatography (80% ethyl acetate/hexane) to give a mixture of the *syn*- and *anti*-diols in the ratio of 2:1. The two alcohols was isolated by preparative TLC (75% ethyl acetate/*n*-hexane) to give *syn*-diol (0.251 g, 45%) and *anti*-diol (0.126 g, 22%) as an oil and a colourless crystalline solid respectively.

3.17. Reduction of **20** with L-selectride

To the stirred solution of the lactol **20** (0.168 g, 0.41 mmol) in dry THF (5 mL) at −78°C was added a solution of L-selectride (5 equiv., 2.03 mmol, 2.03 mL of 1 M solution in THF). After stirring at −78°C for 2.5 days, the reaction mixture was quenched with a solution of 10% NaOH (4 mL) and 30% H_2O_2 (2 mL). The reaction was stirred at rt for another 2 h and was then diluted with a saturated solution of NaCl (2 mL) and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed to give a thick oil which was purified on a preparative TLC plate to give the *anti*- and *syn*-diols, in the ratio of 84:16 (95 mg, 57%), plus unreacted lactol **20** (35 mg).

syn-Diol **22**: ^{1}H NMR δ 7.39 (d, 1H, J=0.9 Hz, H5), 5.05 (d, 1H, J=5.4 Hz, H1′), 4.48 (t, 1H, J=5.7 Hz, H2′), 4.34–4.28 (m, 1H, H3′), 3.91 (dd, 1H, J=5.7, 11.7 Hz, CHaHb), 3.79 (dd, 1H, J=3.9, 11.7 Hz,

CHaHb), 3.24 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 1.70 (s, 3H, CH_3), 1.52 (s, 3H, CH_3CCH_3), 1.38 (s, 3H, CH_3CCH_3); ^{13}C NMR δ 172.41 (C2), 156.24 (C4), 116.51 (C5), 108.33 (CH_3CCH_3), 100.76 ($C(OCH_3)_2$), 79.23 (C1′), 77.54 (C2′), 68.48 (C3′), 60.60 (C4′), 49.40 (OCH_3), 49.36 (OCH_3), 27.30 (CH_3), 25.07 (CH_3CCH_3), 24.30 (CH_3CCH_3); MS (ES +ve) m/z 334.0 (M+1, 70%), 301.9 (M−OCH_3, 100%); $[\alpha]_D^{26}$ −45.0 (c 0.8, CH_2Cl_2). HRMS calcd for $C_{14}H_{24}NO_6S$ 334.13240; found 334.132425. *anti*-Diol **23**: ^{1}H NMR δ 7.29 (d, J=0.6 Hz, H5), 4.98 (dd, 1H, J=5.1, 8.1 Hz, H1′), 4.47 (dd, 1H, J=5.7, 8.1 Hz, H2′), 4.37 (ddd, 1H, J=5.4, 6.9, 6.0 Hz, H3′), 4.25 (d, 1H, J=5.1 Hz, OH), 3.91 (ddd, 1H, J=5.4, 6.9, 12.0 Hz, CHaHb), 3.77 (ddd, 1H, J=4.8, 7.5, 12.0 Hz, CHaHb), 3.52 (dd, 1H, J=6.0, 12.0 Hz, OH), 3.23 (s, 6H, 2×OCH_3), 1.70 (s, 3H, CH_3), 1.46 (s, 3H, CH_3CCH_3), 1.35 (s, 3H, CH_3CCH_3); ^{13}C NMR δ 171.87 (C2), 155.94 (C4), 116.61 (C5), 108.35 (CH_3CCH_3), 100.77 ($C(OCH_3)_2$), 78.83 (C1′), 77.43 (C2′), 68.30 (C3′), 60.62 (C4′), 49.32 (2×OCH_3), 27.70 (CH_3), 25.20 (CH_3CCH_3), 24.14 (CH_3CCH_3); MS (ES +ve) *m/z* 33.9 (M+1, 100%), 301.8 (M−OCH_3, 100%); mp 78–79°C; $[\alpha]_D^{26}$ −28.89 (c 0.9, CH_2Cl_2). Anal. calcd for $C_{14}H_{23}NO_6S$: C, 50.44; H, 6.95; N, 4.20; S, 9.62. Found: C, 50.59; H, 7.06; N, 3.93; S, 9.60%.

*3.18. (1R,2S,3R)-2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)thiazole **3***

To the stirred solution of *syn*-diol **22** (0.67 mg, 0.2 mmol) in ethanol (2 mL) was added a solution of 10% HCl (1 mL). The reaction was left to stir at rt for 2 h. Ethanol was removed under reduced pressure and the aqueous layer was washed with ether. Water was removed under high vacuum to give a pale yellow hydroscopic solid (40 mg, 70%) that was judged to be >95% pure from ^{1}H NMR analysis, $[\alpha]_D^{23}$ −29.83 (c 1.75, H_2O). The spectral data for this compound were identical to those obtained above for the synthesis of **3** from **12**.

*3.19. (1S,2S,3R)-2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)thiazole **24***

To the stirred solution of *anti*-diol **23** (69 mg, 0.21 mmol) in ethanol (2 mL) was added a solution of 10% HCl (1 mL). The reaction was left to stir at rt for 2 h. Ethanol was removed under reduced pressure and the aqueous layer was washed with ether. Water was removed under high vacuum to give a dark yellow solid (53 mg, 90%) that was judged to be >95% pure from ^{1}H NMR analysis. ^{1}H NMR δ (D_2O) 7.66 (s, 1H, H5), 4.89 (d, 1H, J=5.1 Hz, H1′), 3.76 (t, 1H, J=6.0 Hz, H2′), 3.52 (dd, 1H, J=6.0, 13.5 Hz, H3′), 3.39 (m, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (D_2O) δ 193.78 (CO), 165.56 (C2), 156.88 (C4), 124.73 (C5), 73.17 (C1′), 71.36 (C2′), 69.48 (C3′), 61.89 (C4′), 25.29 (CH_3); MS (ES +ve) *m/z* 247.8 (M+1, 35%); $[\alpha]_D^{23}$ +23.64 (c 1.65, H_2O).

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