Selective Formation of 1,3-Oxazolidine-2-thiones on Ketohexose Templates

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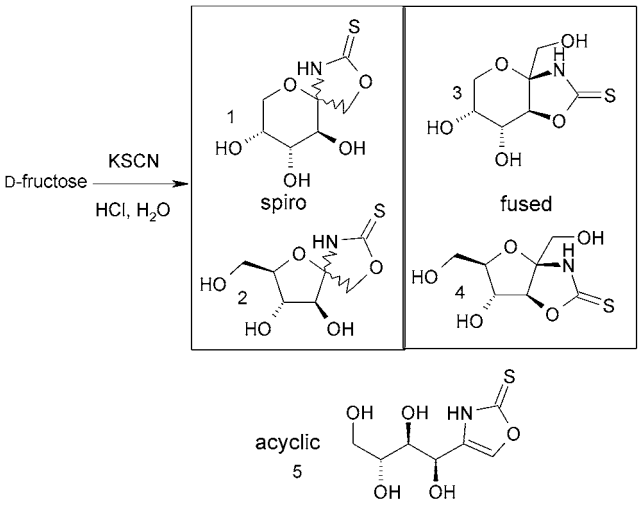
Dedicated to the memory of Professor Christian Pedersen, a gentleman in glycochemistry.

Abstract: Thiocyanic acid condensation on selectively protected ketohexose led to the isolation of five out of the seven possible 1,3-oxazolidine-2-thiones (OZT). The four isomeric spiro-OZT synthesized showed promising biological activity against D-fructose transport.

Key words: carbohydrates, bicyclic compounds, spiro compounds, D-fructose, 1,3-oxazolidine-2-thione

Among chiral auxiliaries, 1,3-oxazolidine-2-thiones (OZT) have attracted important interest because of their various applications in different synthetic transformations.[1] These simple structures, closely related to the popular chiral oxazolidinones,[2] have been explored in asymmetric Diels–Alder reactions and asymmetric alkylations of their *N*-enoyl derivatives, but mostly in condensations of their *N*-acyl derivatives on aldehydes which have shown interesting features in *anti*-selective aldol reactions.[3] All those major advances have proven helpful in the total synthesis of biologically important natural products.[4] In addition, OZT offer some advantages over oxazolidinones – namely high UV absorption or facile N-acylation and -deacylation.[5] Preparation of chiral OZT can easily be performed reacting a β-aminoalcohol with thiophosgene under basic conditions, but some natural chiral oxazolidinethiones can also be produced by controlled myrosinase degradation of glucosinolates like progoitrin.[6] In glycochemistry, OZT have long been studied: preparation is either effected by reacting aminosugars with thiophosgene under basic conditions or condensing thiocyanic acid on unprotected carbohydrates.[7] Fewer developments on the resulting complex bicyclic OZT have been described. Exploration of the synthesis of indolizidine-type iminosugars has been reported through an elegant intramolecular ring closure using the OZT as nitrogen nucleophile.[8] Formation of OZT at the anomeric position of carbohydrates has led to the development of base-modified or sugar-modified nucleosides; it was also exploited to mimic the hexoketose conformations in inhibiting fructose transporter GLUT5.[9] The preparation of OZT on hexoketoses is far from being a trivial reaction despite the simple conditions used (KSCN, HCl, H_2O). Indeed, that reaction can be expected to produce up to seven different OZTs (Scheme 1). Per-O-silylation of standard mixtures resulting from preliminary experiments has shown the fused furano derivative **4** to be the major product (30% yield) from D-fructose. Similarly, L-sorbose afforded a 50% yield of the C-5 epimer of **4**, however no simple reaction allowed a selective and efficient formation of those compounds.[10] With a view to developing better functionalized and more selective GLUT5 inhibitors, the methodology to prepare efficiently various ketohexose-derived OZTs is needed to be developed.



Scheme 1

A selective O-protection of D-fructose would indeed reduce the number of possibilities. 3-O-Protection would only allow formation of the spiro-derivatives **1** and **2** or oxazolinethione **5**, whereas 1-O-protection would only lead to fused structures **3** and **4**. Benzyl protected derivatives were selected as a model to study the selectivity of formation of OZT on a ketohexose structure. The ether protecting group should resist the strongly acidic conditions required to form OZT. Various protected D-fructose derivatives could be readily prepared in reasonable overall yields through classical protection–deprotection glycochemistry, using mainly diisopropylidenation–benzylation procedures. A standard two-step sequence is represented in the following: (1) isopropylidene deprotection (aqueous TFA); (2) condensation with pseudohalogen HSCN produced the OZT (Scheme 2).

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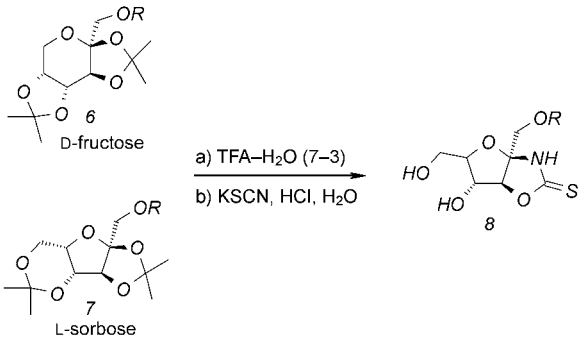
We have previously described the formation of fused derivatives of type **4**, through 1-O-protection with benzyl or allyl groups on either di-*O*-isopropylidene D-fructose or L-sorbose **6** and **7**.[9d] Of the two possible structures expected in the D-fructo series, only the fused furano-OZT **8** was detected and isolated (Scheme 2). This result is consistent with molecular modeling: the enthalpy of formation was calculated using MOPAC parameters, showing a greater stability (>7 kcal/mol) of **4** against **3**.



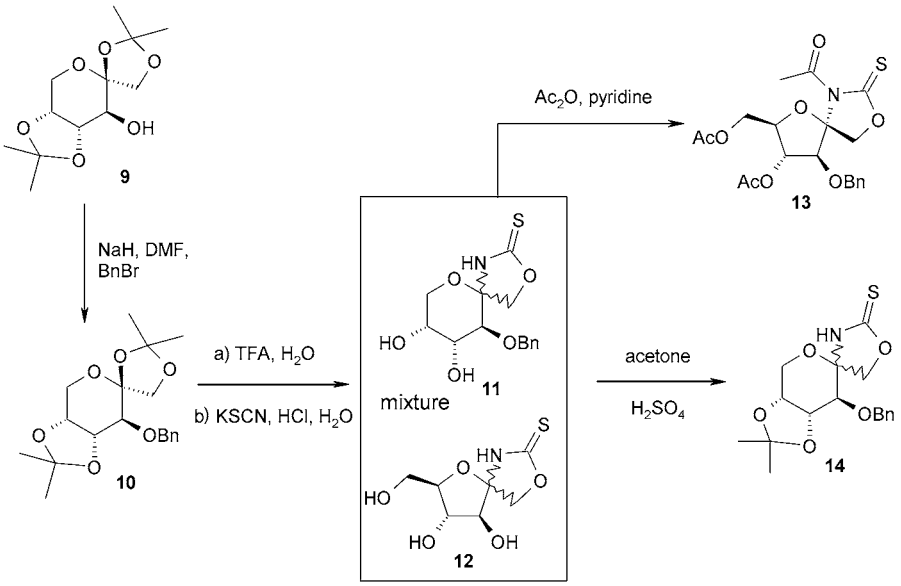
Scheme 2

A 3-O-benzylated D-fructose derivative was produced from 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**9**) under standard conditions[11] to yield compound **10** (Scheme 3). Transient 3-O-benzylated D-fructose resulting from acidic hydrolysis was reacted with thiocyanic acid without intermediate purification. This sequence afforded a mixture of isomeric spiro-OZT **11** and **12**, which was difficult to separate, thus necessitating post-functionalization. Standard acetylation did not improve separability: only the peracetylated α-spiro-furanose **13** could be isolated in 13% yield. In contrast, acetalation with acetone led to a separable mixture of spiro-pyranose derivatives **14**. Both epimers were isolated in a 1:6.5 (α:β) ratio albeit in a moderate 30% yield over the three-step sequence.

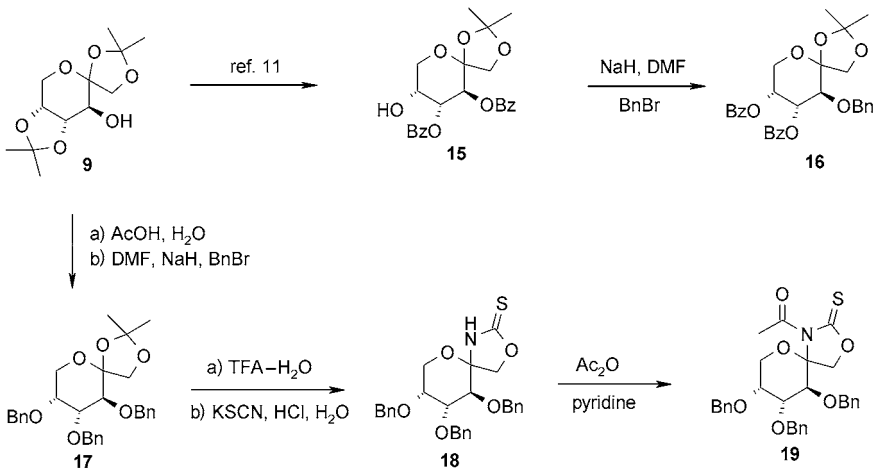
One other possibility to reduce the number of spiranic forms was to prevent the 5-to-2 cyclization resulting into furano derivatives. A 5-O-benzyl derivative would in this case be appropriate, however in our hands, standard approaches to produce a 5-O-benzylated ketohexose failed. Whereas the preparation of the di-O-benzoylated compound **15** was straightforward,[11] all attempts to benzylate the remaining hydroxyl under basic or acidic conditions only resulted in migration of the benzoyl groups and benzylation shifted to the O-3 position to afford compound **16** (Scheme 4).

We therefore turned our attention to the 3,4,5-tri-*O*-benzyl D-fructopyrano derivative **17**, which should lead to the spiro-pyrano forms. Selective deprotection of the 4,5-*O*-isopropylidene of **9**, then perbenzylation gave **17** in 64% overall yield. The expected spiro-pyrano OZT **18** were obtained in reasonable yield of 53%, but the two epimers could only be separated after acetylation with difficulties and rather low yields – 16% (**19β**) and 9% (**19α**) – due to relative instability of the *N*-acetyl spiro-pyrano OZT.

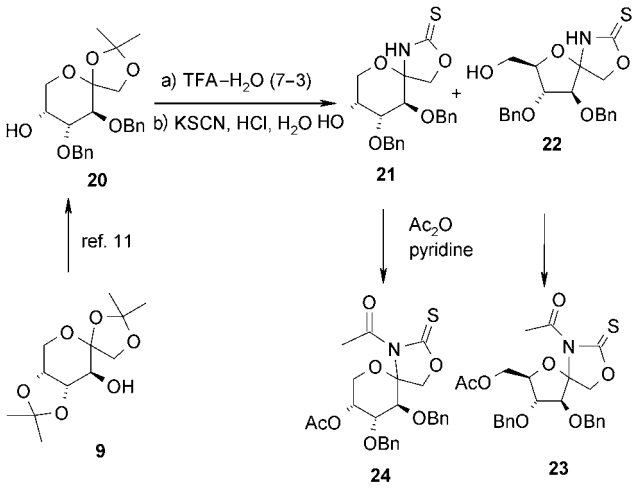
The 3,4-di-O-benzylated D-fructopyrano derivative **20** (Scheme 5) could also be a precursor of choice to form OZT. Readily available through a methodology developed in our group,[11] it would limit the possibilities for spiro-furano and -pyrano derivatives. Application of the usual two-step process afforded, with an overall yield of 60%, a mixture of OZT in which the spiro-furano forms **22** predominated over the spiro-pyrano forms **21** in a 2:1 ratio. After column chromatography separation of **21** from **22**, acetylation allowed isolation of each epimer either furano-**23α** and -**23β** (37% and 35% yield, respectively) or pyrano-**24α** and -**24β** (41% and 27% yield, respectively).[12]



Scheme 3



Scheme 4



Scheme 5

The present study describes the first selective formation of oxazolidinethiones on ketohexose templates with a characterization of five out of the seven possible structures. This will allow development of new inhibitors of the D-fructose transporter GLUT5 built from ketohexose template structures. In a first approach, after isopropylidene removal under acidic conditions of compound **14β**, the resulting 4,5-diol compound was engaged in inhibition tests on CHO cells overexpressing GLUT5: an encouraging inhibition constant of 2.7 mM was measured. This first result is worth comparing to the values previously obtained with 1-O-benzylated derivatives **8** – D-fructo: 32.6 mM, L-sorbo: 17.4 mM – which showed a much lower inhibition potential. The Ki measured for **14β** comparable with best inhibition observed with some oxazolidinones (L-sorbose: 3.1 mM).[9d] Further exploration in GLUT5 transporter inhibition of the structure-activity relationship for all various 1,3-oxazolidine-2-thione and 1,3-oxazolidine-2-thione possibilities on ketohexose templates is under current effort.

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(12) **General Protocol for the Formation of 23 and 24:** 1,2-*O*-Isopropylidene-3,4-di-*O*-benzyl-β-D-fructopyranose **20** (1.1 g, 2.75 mmol) was dissolved in a cooled solution of TFA–H_2O (3:2) and stirred at r.t. overnight. The crude solution was evaporated and co-evaporated with toluene (3 times); the residue was suspended in H_2O containing KSCN (670 mg, 6.87 mmol) and 37% HCl (0.57 mL) was added. The resulting solution was heated for 3 d at 50 °C, then cooled and extracted with EtOAc (3 times). The organic phases were collected and washed with $NaHCO_3$ until neutral, then with brine and dried over $MgSO_4$. The residue obtained after evaporation was purified on column chromatography using petroleum ether–EtOAc (1:1 mixture). Spiro-furano OZT **22** (410 mg, 1.02 mmol, 37% yield) was isolated as the first fraction then spiro-pyrano OZT **21** (250 mg, 0.62 mmol, 22% yield). Each fraction was acetylated (Ac_2O 2 mL, pyridine 5 mL, 24 h); after co-evaporation with toluene, the residue was purified on column chromatography using petroleum ether–EtOAc mixtures (8:2 for furano OZT and 7:3 for pyrano OZT). Spiro-furano OZT **23α** (155 mg, 0.32 mmol, 37% yield) and then **23β** (150 mg, 0.31 mmol, 35% yield) was isolated. Spiro-furano OZT **23α**: $[\alpha]_D^{25}$ +134.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, OAc), 2.70 (s, 3 H, NAc), 3.86 (dd, 1 H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 9.1 Hz, H-4), 3.95 (dd, 1 H, $J_{5,6b}$ = 4.4 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 4.14 (d, 1 H, $J_{1a,1b}$ = 10.0 Hz, H-1b), 4.22 (dd, 1 H, $J_{5,6a}$ = 2.3 Hz, H-6a), 4.46 (ddd, 1 H, H-5), 4.50 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.63 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.63 (d, 1 H, *J* = 11.7 Hz, CH_2Ph), 4.73 (d, 1 H, *J* = 11.7 Hz, CH_2Ph), 4.94 (d, 1 H, H-1a), 5.09 (d, 1 H, H-3), 7.23–7.38 (m, 10 H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.7 (OAc), 28.0 (NAc), 62.9 (C-6), 72.9 (CH_2Ph), 73.6 (C-1), 74.0 (CH_2Ph), 78.0 (C-5), 80.9 (C-4), 83.3 (C-3), 100.5 (C-2), 127.9, 128.2, 128.4, 128.6, 128.7, 128.9, 136.6, 137.4 (C-Ar), 170.4 (CO), 172.1 (CO), 185.7 (CS). MS (IS+): *m/z* = 508.0 $[M + Na]^+$, 486 $[M + H]^+$, 466.0 $[M – Ac + Na]^+$. Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.61; N, 2.89. Found: C, 61.61; H, 5.59; N, 2.88. Spiro-furano OZT **23β**: $[\alpha]_D^{25}$ +7.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.07 (s, 3 H, OAc), 2.75 (s, 3 H, NAc), 4.05 (d, 1 H, $J_{1a,1b}$ = 10.1 Hz, H-1b), 4.11 (ddd, 1 H, $J_{4,5}$ = 7.5 Hz, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 7.6 Hz, H-5), 4.20 (d, 1 H, $J_{3,4}$ = 6.5 Hz, H-3), 4.31 (dd, 1 H, $J_{6a,6b}$ = 11.8 Hz, H-6b), 4.41 (d, 1 H, H-1a), 4.43 (dd, 1 H, H-6a), 4.53 (dd, 1 H, H-4), 4.55 (d, 1 H, *J* = 11.7 Hz, CH_2Ph), 4.60 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.66 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.68 (d, 1 H, *J* = 11.7 Hz, CH_2Ph), 7.21–7.40 (m, 10 H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.0 (OAc), 27.6 (NAc), 65.1 (C-6), 73.2 (CH_2Ph), 73.6 (CH_2Ph), 77.6 (C-1), 80.9 (C-5), 84.2 (C-4), 87.1 (C-3), 99.5 (C-2), 127.8, 128.2, 128.3, 128.7, 128.9, 136.6, 137.5 (C-Ar), 171.0 (CO), 172.7 (CO), 186.4 (CS). MS (IS+): *m/z* = 508.0 $[M + Na]^+$, 466.0 $[M – Ac + Na]^+$. Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.61; N, 2.89. Found: C, 61.48; H, 5.81; N, 2.63.

Spiro-pyrano OZT **24β** (50 mg, 0.10 mmol, 27% yield) and then **24α** (75 mg, 0.15 mmol, 41% yield) were also isolated. Spiro-pyrano OZT **24β**: $[\alpha]_D^{25}$ –98 (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.12 (OAc), 2.68 (NAc), 3.76 (d, 1 H, $J_{3,4}$ = 8.8 Hz, H-3), 3.90 (dd, 1 H, $J_{5,6b}$ = 2.6 Hz, $J_{6a,6b}$ = 12.7 Hz, H-6b), 4.06 (d, 1 H, $J_{1a,1b}$ = 9.6 Hz, H-1b), 4.38 (d, 1 H, H-1a), 4.41 (dd, 1 H, $J_{5,6a}$ = 1.3 Hz, H-6a), 4.42 (dd, 1 H, $J_{4,5}$ = 3.9 Hz, H-4), 4.49 (d, 1 H, *J* = 10.6 Hz, CH_2Ph), 4.60 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.69 (d, 1 H, *J* = 10.6 Hz, CH_2Ph), 4.92 (d, 1 H, *J* = 10.6 Hz, CH_2Ph), 5.51 (m, 1 H, H-5), 7.16–7.37 (m, 10 H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.2 (OAc), 28.0 (NAc), 66.1 (C-6), 67.3 (C-5), 71.8 (CH_2Ph), 75.6 (C-3), 77.1 (C-4), 78.5 (C-1), 97.7 (C-2), 127.8, 128.1, 128.3, 128.6, 128.7, 137.3, 137.5 (C-Ar), 170.4 (CO), 174.7 (CO), 187.9 (CS). MS (IS+): *m/z* = 508.0 $[M + Na]^+$, 466.0 $[M – Ac + Na]^+$, 444.0 $[M – Ac + H]^+$. Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.61; N, 2.89. Found: C, 61.68; H, 5.48; N, 2.85. Spiro-pyrano OZT **24α**: $[\alpha]_D^{25}$ +45.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, OAc), 2.65 (s, 3 H, NAc), 3.45 (dd, 1 H, $J_{4,3}$ = 10.2 Hz, $J_{4,5}$ = 2.1 Hz, H-4), 3.57 (dd, 1 H, $J_{5,6b}$ = 1.3 Hz, $J_{6a,6b}$ = 14.0 Hz, H-6b), 4.04 (dd, 1 H, $J_{5,6a}$ = 1.3 Hz, H-6a), 4.38 (d, 1 H, $J_{1a,1b}$ = 9.3 Hz, H-1b), 4.54 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.59 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.73 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 4.76 (d, 1 H, H-1a), 4.85 (d, 1 H, *J* = 11.4 Hz, CH_2Ph), 5.06 (d, 1 H, H-3), 5.34 (m, 1 H, H-5), 7.21–7.33 (m, 10 H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.2 (OAc), 28.1 (NAc), 64.0 (C-6), 66.9 (C-5), 70.6 (C-1), 72.0 (*C*H_2Ph), 73.6 (C-3), 75.7 (CH_2Ph), 78.2 (C-4), 97.3 (C-2), 127.9, 128.1, 128.2, 128.6, 137.3, 137.6 (C-Ar), 170.7 (CO), 172.0 (CO), 186.7 (CS). MS (IS+): *m/z* = 508.0 $[M + Na]^+$, 466.0 $[M – Ac + Na]^+$, 444.0 $[M – Ac + H]^+$. Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.60; N, 2.88. Found: C, 61.72; H, 5.57; N, 2.88.