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A concise route to tiazofurin

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Abstract—Successful oxidation of a key thiazoline intermediate allows an efficient synthesis of tiazofurin in four steps from commercially available 1′-acetoxy-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose.

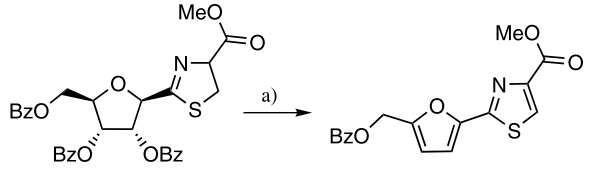
Tiazofurin **4**[1] is converted in vivo into the active metabolite thiazole-4-carboxamide adenine dinucleotide (TAD), an analogue of NAD that prevents de novo guanine nucleotide synthesis via inhibition of inosine monophosphate dehydrogenase (IMPDH, EC 1.1.1.205).[2] The consequent decrease in cellular GTP and deoxyGTP concentrations interrupts DNA and RNA synthesis in rapidly-dividing tumour cells. Tiazofurin proved effective in reducing the leukaemic cell burden in acute myelogenous leukaemia patients, but was found to be too toxic for general clinical application.[3–5] Subsequent discovery of two IMPDH isoforms, of which type II is up-regulated in human leukaemia cell lines,[6,7] has prompted studies to inform the design of isoform selective inhibitors[8] and has renewed interest in tiazofurin and its analogues.[9,10]

Several routes have been published toward this compound; of these the preparation reported by Ramasamy and co-workers[11] provides tiazofurin, while avoiding the use of hydrogen sulfide gas. These authors reported unsuccessful oxidation of thiazoline **1** with MnO_2, or a range of other conditions, observing elimination of the 2′,3′-benzoate esters to afford thiazole-furan **2** in each case (Scheme 1).

Instead, isopropylidene **3** was converted into the target compound **4** with good reported yields, but the introduction and removal of the isopropylidene protecting group introduced an extra three steps from 1′-acetoxy-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose **5** (Scheme 2).

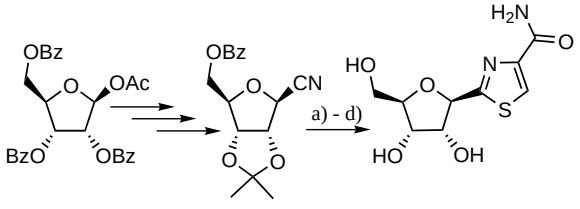
We now report the successful oxidation of thiazoline **1** that removes the need for this detour and reduces the synthesis of tiazofurin to a simple four-step procedure.

Thiazoline **1** was prepared by reaction of 1′-cyano-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose[12] with L-cysteine methyl ester in the presence of triethylamine according to an established protocol.[11] Complete epimerisation of the cysteine α-proton was observed by ^1H NMR, but this centre will become part of the aromatic thiazole. A number of oxidation conditions, including DDQ in toluene,[13] did not proceed to our satisfaction, but we were pleased to observe clean conversion of the thiazoline **1** in the presence of bromotrichloromethane and DBU.[14] Thiazole **6** was thus prepared from commer-



1 **2**

Scheme 1. *Reagents and conditions*:[11] (a) MnO_2/benzene/reflux.



5 **3** **4**

Scheme 2. *Reagents and conditions*:[11] (a) cysteine ethyl ester·HCl/Et_3N; (b) MnO_2/benzene/reflux; (c) 90% TFA; (d) NH_3/MeOH.

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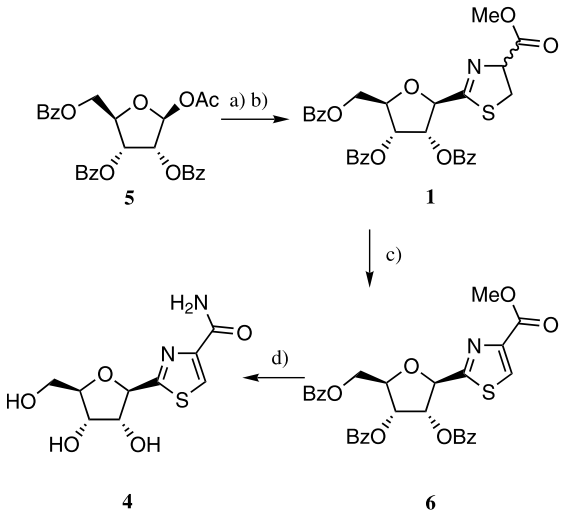

Scheme 3. *Reagents and conditions*: (a) TMSCN, $SnCl_4$, CH_2Cl_2, rt, 2 min; (b) L-cysteine methyl ester hydrochloride, Et_3N, CH_2Cl_2; (c) $BrCCl_3$, DBU, CH_2Cl_2, 0°C, 61% over three steps; (d) NH_3/MeOH, rt, 20 h, 86%.

cially available 1′-acetoxy-2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranose **5** in an unoptimised isolated yield of 61% over the three steps with just one chromatographic separation (Scheme 3).[15]

Ester aminolysis and global deprotection were effected by stirring **6** in methanolic ammonia.[16] Dissolution of the concentrated crude reaction mixture into water and extraction of all contaminants into ethyl acetate proved sufficient to afford pure tiazofurin **4** in 86% yield.

In summary, selective dehydrogenation of a thiazoline **1** in the presence of sensitive ribose 2′,3′,5′-tribenzoate ester protecting groups is described. The immediate benefit of this discovery is to improve the efficiency of tiazofurin synthesis in the absence of hydrogen sulfide affording a productive four-step protocol.

Acknowledgements

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15. **Preparation of methyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazole-4-carboxylate 6**. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (2.4 mL, 16 mmol, 2 equiv.) was added to a stirred solution of methyl 1′-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazoline-4′-carboxylate **1** (4.7 g, 8 mmol) in CH_2Cl_2 (250 mL). The solution was cooled to 0°C and $BrCCl_3$ (1.9 g, 9 mmol, 1.0 mL) was added dropwise and the resulting mixture stirred overnight. The reaction mixture was then concentrated, dissolved into ethyl acetate and the solution washed 3× with satd aq. NH_4Cl. The organic layer was dried (Na_2SO_4), filtered, concentrated and subject to column chromatography on silica gel using a gradient of hexane:ethyl acetate from 9:1 to 7:3 as eluent to afford **6** as a light yellow foam. Yield 3.6 g, 6.1 mmol, 61% over three steps. $[\alpha]_D^{25}$ −43.3 (*c* 1, $CHCl_3$); IR (KBr) 1726, 1269, 1095, 710 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$): δ 8.15 (1H, s, SCH) 8.09–8.07 (2H, m, Ar-H) 8.00–7.97 (2H, m, Ar-H) 7.92–7.87 (2H, m, Ar-H) 7.58–7.51 (3H, m, Ar-H) 7.45–7.33 (6H, m, Ar-H) 5.91–5.88 (2H, m, H-2′,3′) 5.75 (1H, d, J=4.7, H-1′) 4.89 (1H, dd, J=12.1, 3.1, H-5′a) 4.75–4.78 (1H, m, H-4′) 4.61 (1H, dd, J=12.1, 3.9, H-5′b) 3.91 (3H, s, $COOCH_3$); ^{13}C NMR (100 MHz (DEPT) $CDCl_3$): δ 169.6(0), 166.2(0), 165.3(0), 165.2(0), 161.6(0), 147.3(0), 133.8(1), 133.7(1), 133.5(1), 130.1(1), 129.92(1), 129.91(1), 129.6(0), 128.98(0), 128.92(0), 128.76(1), 128.7(1), 128.6(1), 80.9(1), 80.8(1), 76.9(1), 72.5(1), 64.0(2), 52.8(3). MS (FAB$^+$) m/z (M+H)$^+$ 588 (100). MS (FAB$^+$/HR) m/z (M+H)$^+$ calcd for $C_{31}H_{25}NO_9S$: 588.1329. Found: 588.1341.
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