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SYNTHESIS OF 2-β-D-ARA- AND 2-β-D-XYLOFURANOSYLTHIAZOLE-4-CARBOXAMIDE

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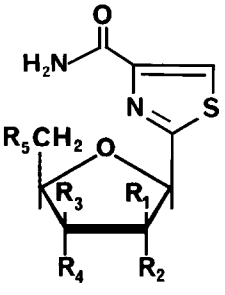
Abstract: The syntheses of the heretofore unknown 2-β-D-ara and 2-β-D-xylofuranosyl isomers of the antitumor agent tiazofurin have been accomplished. In both cases the stereospecific inversion of the required 2' or 3'-hydroxyl group in the protected parent compound afforded the desired products.

In 1982 it was reported that 2-β-D-ribofuranosylthiazole-4-carboxamide (tiazofurin, TR, 1a) was a high-priority antitumor agent candidate with potential for the treatment of lung tumors and metastases.[1] Since that time, this compound has been the subject of numerous studies and it is currently undergoing phase I clinical trials.[2-9]

From the initial work performed by Jayaram et al.[2], it was shown that the 5'- and 2'-deoxyribofuranoside derivatives, 1b and 1c, were non-cytotoxic to P388 cells in culture possibly due to the lack of formation of the required 5'-phosphate metabolites.[2] While this appeared obvious in the case of the 5'-deoxy analog (1b), the inertness of the 2'-deoxy derivative (1c) suggested that the enzyme responsible for the phosphorylation of 1a was probably very specific. This specificity was considered worthy of further studies, especially after the 3'-deoxy analog (1d) was confirmed to be cytotoxic against P388 leukemia in vitro.[10] Therefore, in order to delineate further the structural requirements of the sugar moiety, the synthesis of the corresponding ara- and xylofuranosyl analogs of tiazofurin (1e and 1f) was undertaken.



	R1	R2	R3	R4	R5	
1a,	H	OH	H	OH	OH	(TR)
b,	H	OH	H	OH	H	(5'-dTR)
c,	H	H	H	OH	OH	(2'-dTR)
d,	H	OH	H	H	OH	(3'-dTR)
e,	OH	H	H	OH	OH	(ara-T)
f,	H	OH	OH	H	OH	(xylo-T)

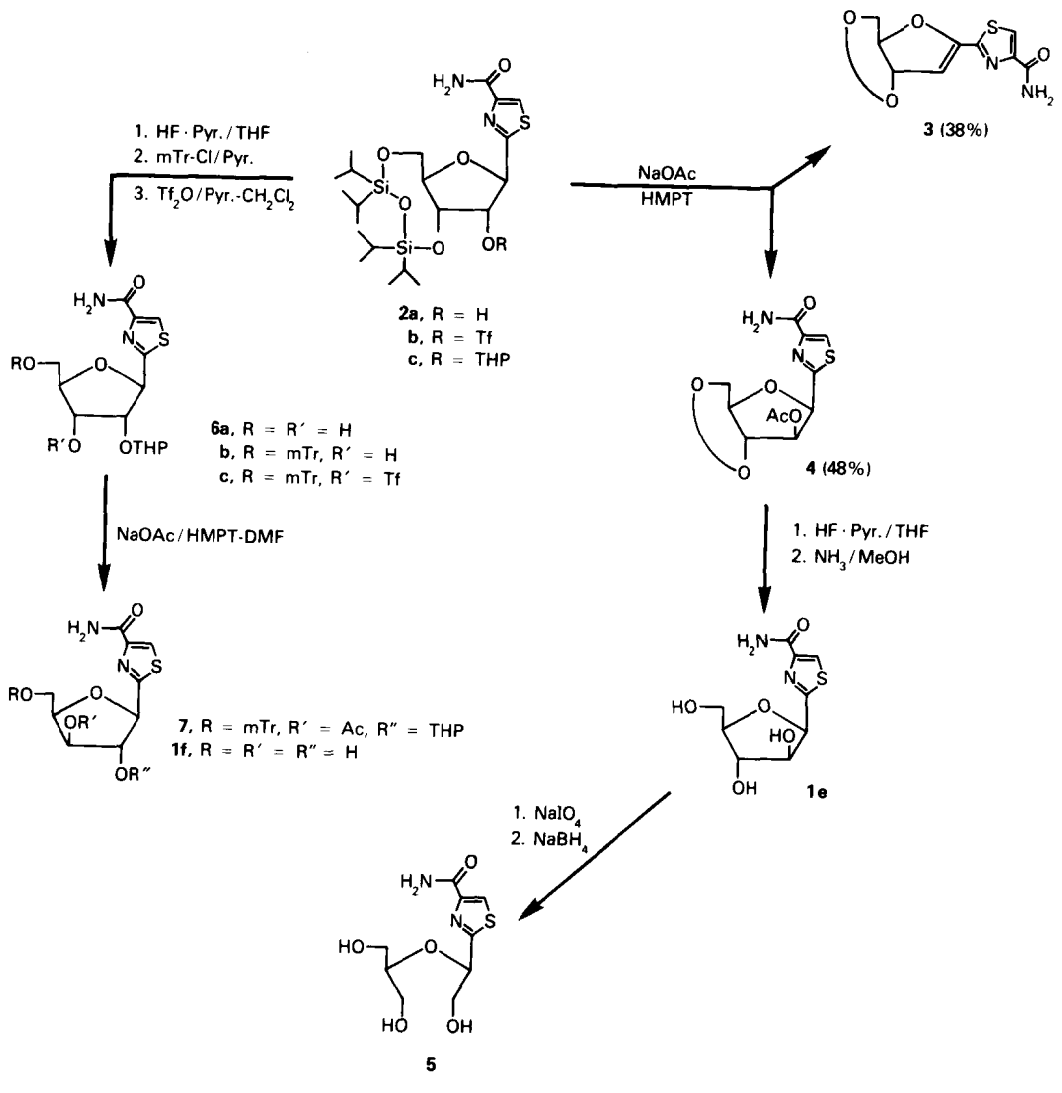
Two possible synthetic approaches were initially considered: (A) the construction of the thiazole ring from the correspondingly protected cyano sugars in the manner reported for the synthesis of 1a and 1c, [11-13] or (B) the specific inversion of the appropriate hydroxyl group in tiazofurin (1a). The latter methodology appeared preferable in order to avoid the formation and separation of undesired α-anomers.

Early attempts to reach our objective arabinosyl derivative (1e) via the corresponding 2'-keto nucleoside, according to the methodology of Robins,[14] were hampered by the unexpected resistance to oxidation exhibited by the protected 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-tiazofurin intermediate (2a). Therefore, we approached these compounds by nucleophilic displacement and consequent inversion of configuration of the specifically generated 2'-O- or 3'-O-triflates of tiazofurin (2b and 6c) as shown in Scheme 1.

Simultaneous protection of the 3'- and 5'-hydroxyl groups was accomplished by reacting equivalent amounts of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSiCl)[15] with 1a (-20° → rt, 3 h) to afford 78% yield of 2a. For the preparation of the arabinose analog, 2a was treated with trifluoromethanesulfonic anhydride (Tf_2O) in a mixture of pyridine and methylene chloride (0°, 3 h) to give the 2'-O-triflate (2b) in 70% yield. Reaction of 2b with NaOAc in hexamethylphosphoric triamide (HMPT, rt, 20 h) gave 48% yield of the desired compound 4 plus 38% yield of the elimination product 3. Base-catalyzed eliminations of this type in C-nucleosides have been reported previously by Moffatt et al.[16] Conventional attempts to deprotect 4 with tetrabutylammonium fluoride gave rise to an unseparable mixture. Successful deblocking of compound 4 was finally accomplished by the use of HF/pyridine[17] (rt, 2 days) and the resulting compound was immediately treated with methanolic ammonia to generate the desired target compound ara-T (1e). In the NMR spectrum the characteristic anomeric proton for ara-T was observed at δ 5.47 (d, J = 4 Hz). This value is 0.31 ppm lower than the corresponding anomeric proton of tiazofurin.

The observed base-catalyzed elimination that produced compound 3 in this sequence raised the possibility of an accompanying anomerization at C-1' in the resulting product 4. Therefore, it became necessary to unambiguosly demonstrate the β-configuration of the final target 1e. Using a procedure developed earlier by Khorana et al.,[18] both tiazofurin (1a) and ara-T (1e) were oxidized with $NaIO_4$. As expected, the reaction with ara-T was much slower than that of tiazofurin. The dialdehydes obtained were immediately reduced with $NaBH_4$ and the optical rotations of the resulting alcohols (5) were measured. The $[\alpha]_D^{25}$ values obtained from 1a and 1e were identical (+73.2° ± 2), confirming the correct anomeric configuration for ara-T.

For the preparation of the second target compound, xylo-T (1f), the intermediate 2a was further protected as the 2'-tetrahydropyranyl ether 2c in the usual manner after reacting with 3.0 equivalents of dihydropyran in methylene chloride and pyridinium p-toluenesulfonate (rt, 1 day).[19] As performed in the ara-T sequence, the 3',5'-protective group was removed with HF/Pyridine in tetrahydrofuran (rt, 1 day) and the resulting free 5'-hydroxyl group of 6a protected as the methoxytrityl derivative 6b in the usual manner (2.5 equiv. of trityl chloride, rt, 4 h). The overall yield of these three steps was 52%. Having only the 3'-hydroxyl group free in 6b, reaction with 1.0 equivalent of Tf_2O in pyridine and methylene chloride (-20° → 0°, 4 h) afforded compound 6c in 70% yield. Displacement of the 3'-O-triflate with NaOAc in HMPT/DMF (rt, 20 h) proceeded very efficiently to give compound 7 in 97% yield. Deprotection with methanolic ammonia followed by treatment with 80% acetic acid at rt, produced the desired 1f in quantitative yield. In the NMR spectrum the anomeric proton for xylo-T was observed at δ 5.20 (d, J = 3 Hz), just 0.04 ppm lower than the corresponding tiazofurin signal. Both target compounds were additionally characterized by elemental and mass spectral analyses.[20]


1. HF · Pyr. / THF
2. mTr-Cl/Pyr.
3. Tf_2O/Pyr.-CH_2Cl_2
NaOAc
HMPT
3 (38%)
2a, R = H
b, R = Tf
c, R = THP
6a, R = R′ = H
b, R = mTr, R′ = H
c, R = mTr, R′ = Tf
4 (48%)
NaOAc / HMPT-DMF
1. HF · Pyr. / THF
2. NH_3 / MeOH
7, R = mTr, R′ = Ac, R″ = THP
1f, R = R′ = R″ = H
1e
1. $NaIO_4$
2. $NaBH_4$
5

SCHEME 1

When P388 cells in culture were exposed to these compounds the ID_{50} values were respectively 460 and 800 μM for the ara-T (1e) and xylo-T (1f) analogs contrasting with the average value of 8.4 ± 2.3 μM obtained for TR (1a). This data clearly indicates that the structural requirements of the sugar moiety are indeed extremely rigorous and suggest that perhaps these changes translate into major conformational alterations that deviate from the ideal conformation present in the ribose-bearing compound.

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20. Both ara-T and xylo-T gave the expected MH^+ peak at m/z 261 in the FAB mass spectrum. Elemental analyses for both samples were within ± 0.4% for C, H, N, S.

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