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An efficient approach to enantiomeric isoxazolidinyl analogues of tiazofurin based on nitrone cycloadditions

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Abstract—An efficient synthetic route to isoxazolidinyl analogues of tiazofurin has been developed. The strategy involves, as a key step, a 1,3-dipolar cycloaddition between acrylonitrile and chiral nonracemic nitrones. An opposite diastereofacial induction was observed when the chiral group was placed at either the carbon atom or the nitrogen one of the nitrone function. The 2-cyano isoxazolidines obtained were further converted into the enantiomeric target compounds by constructing the thiazole ring via condensation with L-cysteine.

1. Introduction

Tiazofurin **1a** is a thiazole-containing C-nucleoside, which has demonstrated significant activity in vitro against a number of model tumor systems.[1] In the search for new antiviral and anticancer agents several modifications of nucleosides have been extensively studied.[2] Among these modifications, substitution of the carbohydrate moiety with a different heterocyclic ring has emerged as an outstanding approach to new chiral candidates.[3]

Several structural analogues of tiazofurin have been synthesized with variations in the furanose ring, including preparation of azatiazofurin **1b**[4] and its thio analogue **2**,[5] in which the thiazole ring was replaced by a thiophene ring. The incorporation of additional heteroatoms into the sugar framework[6] has also been investigated by Chu et al.[7] by preparing the dioxolanyl analogue **3**. In order to study the influence of an additional nitrogen atom on the biological activity of nucleosides, we have undertaken a program of synthesis of new isoxazolidinyl nucleosides[8] including the isoxazolidinyl analogue of tiazofurin **4**.[9] (Chart 1).

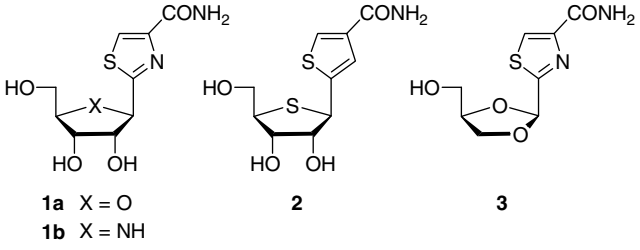

Chart 1. Nucleoside analogues of tiazofurin.

Following this project, we planned the design and synthesis of the isoxazolidinyl analogues of tiazofurin **5** and *ent*-**5** (regioisomers of **4**), in which the relative disposition between the endocyclic oxygen atom and the thiazole ring is the same as that in tiazofurin **1a**. Such a disposition was crucial for the activity as it has been demonstrated by several structural and computational studies (Chart 2).[10]

Herein, we wanted to report model syntheses of the enantiomeric isoxazolidinyl analogues **5** and a *trans*-isomer.

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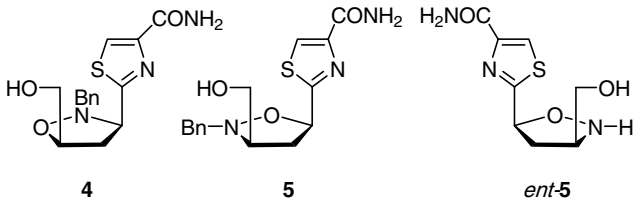
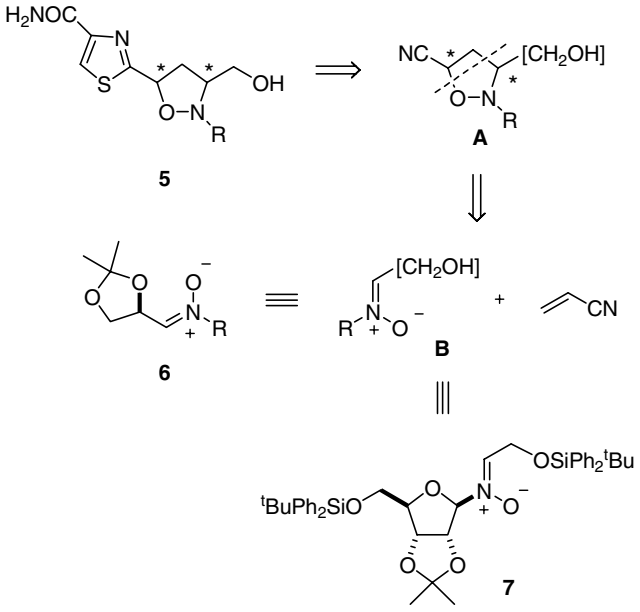


Chart 2. Isoxazolidinyl analogues of tiazofurin.

Our retrosynthetic analysis for the synthesis of **5** is depicted in Scheme 1.



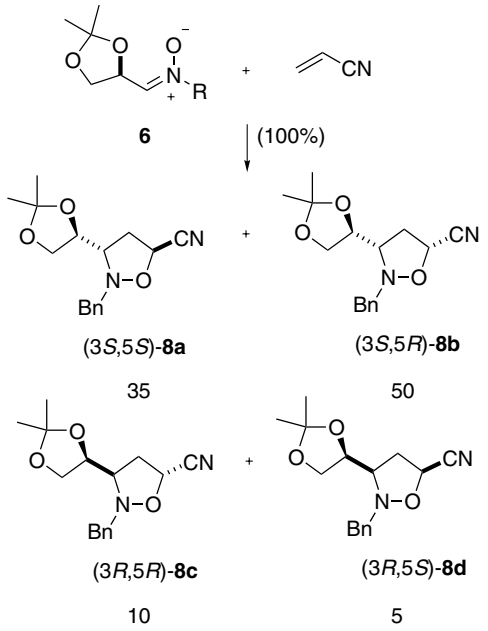
Scheme 1. Retrosynthetic analysis of isoxazolidinyl tiazofurin **5**.

Based on this analysis the thiazole ring was anticipated to be constructed through the use of classical methods[11] from 5-cyanoisoxazolidine **A**, which in turn was anticipated to be derived from the 1,3-dipolar cycloaddition reaction (1,3-DCR) between nitrone **B** and acrylonitrile. Application of this method requires that this cycloaddition reaction proceeds in both an efficient and stereoselective manner, to afford the desired isoxazolidine **A**. The configuration of the newly generated stereogenic centers would be determined by the nitrone. Asymmetric induction in 1,3-DCR has been efficiently achieved by using nitrones with chiral groups at either the nitrogen atom[12] or the carbon atom.[13] As a representative example of the latter approach, *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone **6** (BIGN) is of exceptional usefulness for further conversion of the dioxolane moiety into the hydroxymethyl group.[14] Alternatively, nitrone **7** also constitutes a rather convenient starting material, since all protecting groups, including the carbohydrate unit acting as a chiral auxiliary, can be removed simultaneously.[15] The use of a related *N*-ribosyl nitrone has been described by Vasella in similar cycloaddition reactions.[16] Herein, we report two complementary approaches to tiazofurin analogues **5** and *ent*-**5** using both **6** and **7** as starting materials, respectively.

2. Results and discussion

2.1. Synthesis from *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone 6

The 1,3-dipolar cycloaddition between **6** and acrylonitrile afforded four isomeric isoxazolidines in a 35:50:10:5 ratio and quantitative yield (Scheme 2). The reaction was carried out without solvent and at reflux. No significant changes in the stereoselectivity were observed by decreasing the reaction temperature to 0 °C although the reaction time did increase considerably. In fact, the reaction did not go on completion at ambient temperature after 7 days. The addition of a solvent (CH_2Cl_2, $CHCl_3$, or toluene) also increased the reaction time.



Scheme 2. 1,3-Dipolar cycloaddition between **6** and acrylonitrile.

The relative *cis*/*trans*-configuration of the isoxazolidine ring substituents was assigned on the basis of NOE experiments (Fig. 1). For *trans*-compounds **8a** and **8c**, irradiation of H-3 produced a strong enhancement of only H-4a (18–20%) while irradiation of H-5 produced enhancement of only H-4b (13–16%). Furthermore, irradiation of H-4a and H-4b in the same experiment produced enhancements of H-3 (12–13%) and H-5 (10–12%), respectively. For *cis*-compounds **8b** and **8d**, irradiation of H-4a produced strong enhancements of both H-3 (12–15%) and H-5 (9–11%). Irradiation of H-5 produced enhancement of H-4a (12–14%) and a much smaller enhancement of H-4b (2%, not indicated in Fig. 1). Irradiation of H-3 only produced enhancement of H-4a (11–13%).

The absolute configuration was assigned by determining the relative configuration between isoxazolidine and the

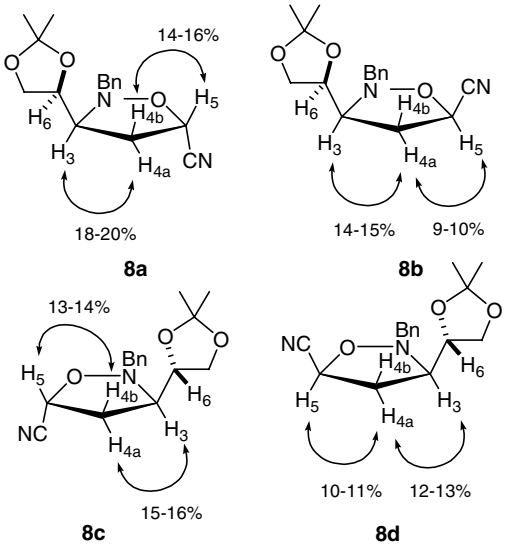


Figure 1. Selected NOE observed for **7** (η_{obs} given as percent of η_{max}).

1,3-dioxolane ring. The assigned configurations were deduced from 2D COSY, NOESY, and HMQC experimental data. In the case of (3*R*,5*S*)-**8d** a single X-ray crystallographic analysis[17] served to confirm its configuration (Fig. 2). This assignment also served to confirm the absolute configuration of the other *cis* adduct, **8b** (the major one obtained in the reaction).

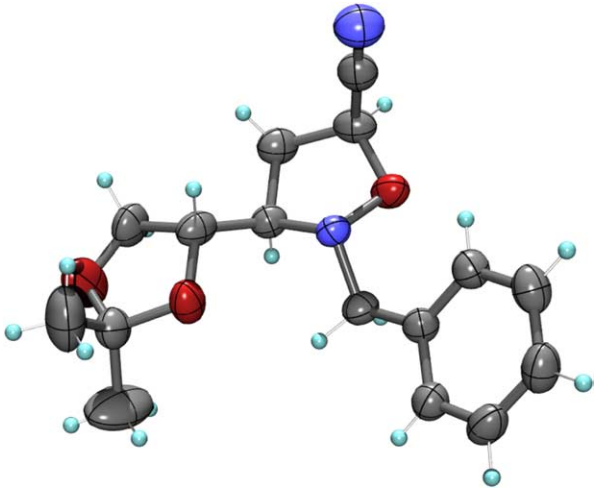


Figure 2. Perspective view (ORTEP) of **8d**. Non-hydrogen atoms are drawn as 50% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principal axes indicated; the isotropic atoms are represented as simple circles.

The reaction showed a good diastereofacial selectivity (*anti*/*syn*, 85:15) but a poor *endo*/*exo* selectivity (*trans*/*cis*, 45:55).[18] The former was in agreement with previous 1,3-dipolar cycloaddition reactions carried out with α-alkoxy nitrones derived from D-glyceraldehyde, in which the *anti* adducts (with respect to the dioxolane ring) were, in all cases, obtained preferentially.[19] The lack of *endo*/*exo* selectivity was also in accordance with previous experimental and theoretical studies carried out by Rastelli et al.[20] Indeed, we have carried out theoretical studies for the particular cycloaddition of **6** and acrylonitrile at B3LYP/6-31G(d) and MP2/6-31+G(d)//B3LYP/6-31G(d) levels[21] and no determinant data could be obtained. The energy values obtained for the transition structures leading to the adducts **8a**–**d** are given in Table 1, while the optimized geometries [B3LYP/6-31G(d)] are illustrated in Figure 3.

Table 1. Total (hartrees) and relative (kcal/mol) electronic energy values for transition structures **TS1**–**TS4**

	Total energy (hartrees)		Relative energy (kcal)	
	E (B3LYP)[a]	*E* (MP2)[b]	*E* (B3LYP)[a]	*E* (MP2)[b]
TS1[c]	−725.452149	−723.494779	0.000	0.000
TS2[d]	−725.451839	−723.494564	0.195	0.129
TS3[e]	−725.449344	−723.491413	1.760	2.107
TS4[f]	−725.449192	−723.491186	1.856	2.249

[a] Optimized structures at B3LYP/6-31G(d) level.
[b] Single point calculations at MP2/6-31G(d)//B3LYP/6-31G(d) level.
[c] *Si endo* leading to *anti trans* **8a**.
[d] *Si exo* leading to *anti cis* **8b**.
[e] *Re endo* leading to *syn trans* **8c**.
[f] *Re exo* leading to *syn cis* **8d**.

Although the calculations correctly predicted the diastereofacial *Si* face preference for the reaction, differences of less than 0.2 kcal/mol were obtained between the corresponding *endo* (**TS1**) and *exo* (**TS2**) transition states. Clearly, these differences are only indicative that mixtures of compounds will be obtained. The values shown in Table 1 cannot be used as predictive values since they are within experimental error.

The formation of the thiazole ring was accomplished by condensation of **8b** with L-cysteine to form the precursor 2-thiazoline following the procedure described by Ramasamy et al.[22] After purification of the reaction mixture we observed epimerization of the stereogenic center at the thiazolidine ring, the two diastereomers of compound **9a** being inseparable. We also obtained methyl ester **9b** in 6% yield due to transesterification with the solvent of the reaction (MeOH). In this case, only one isomer was observed. For synthetic purposes neither the epimerization of **9a** nor transesterification to **9b** are relevant. Oxidation of epimeric **9a** with manganese dioxide yielded the thiazole-containing derivative **10a** (Scheme 3). Transformation of the dioxolane ring into a hydroxymethyl group following our previously reported procedure[23] afforded compound **11a** in 74% overall yield (three steps). During this procedure, we changed to EtOH as the solvent in the deacetalyzation step, in order to avoid further transesterification reaction. Treatment of **11a** with methanolic ammonia quantitatively afforded isoxazolidinyl tiazofurin **5** (47% overall yield; seven steps from nitrone **6**). As stated above, the obtention of a transesterified compound **9b** was not relevant from a synthetic point of view, since that compound was also transformed into **5** following the same sequence of reactions indicated in Scheme 3.

In a similar fashion, the epimeric *trans* adduct **8a** was converted to the *trans*-isomer of isoxazolidinyl analogue

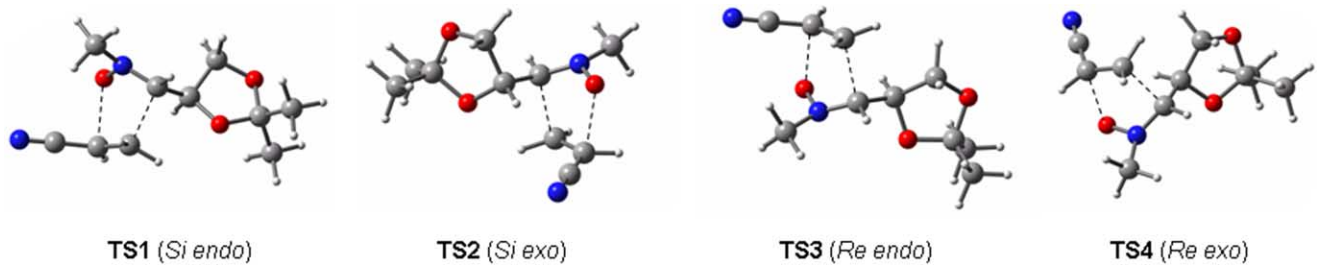
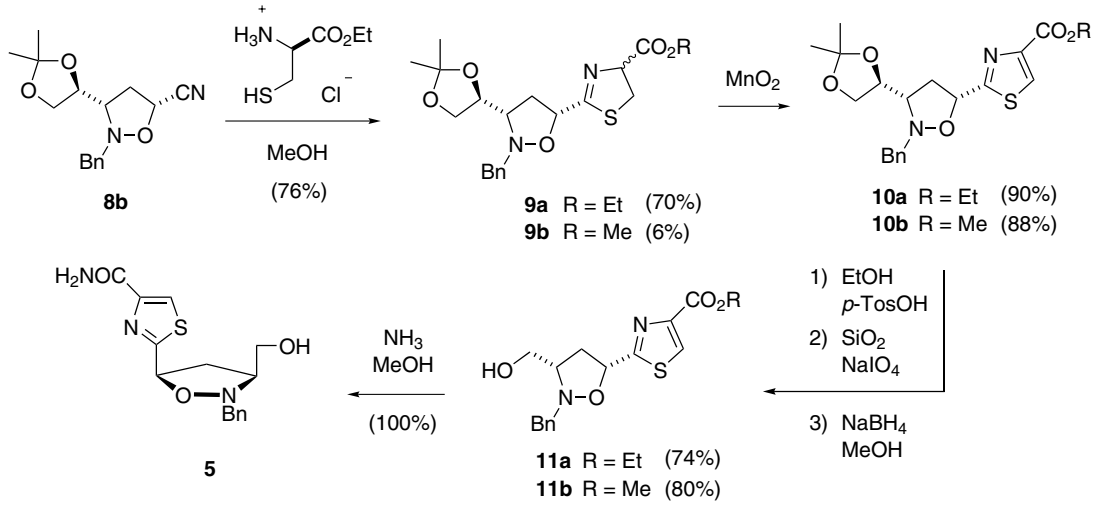


Figure 3. Optimized structures [B3LYP/6-31G(d)] for transition structures leading to adducts **8a**–**d**.

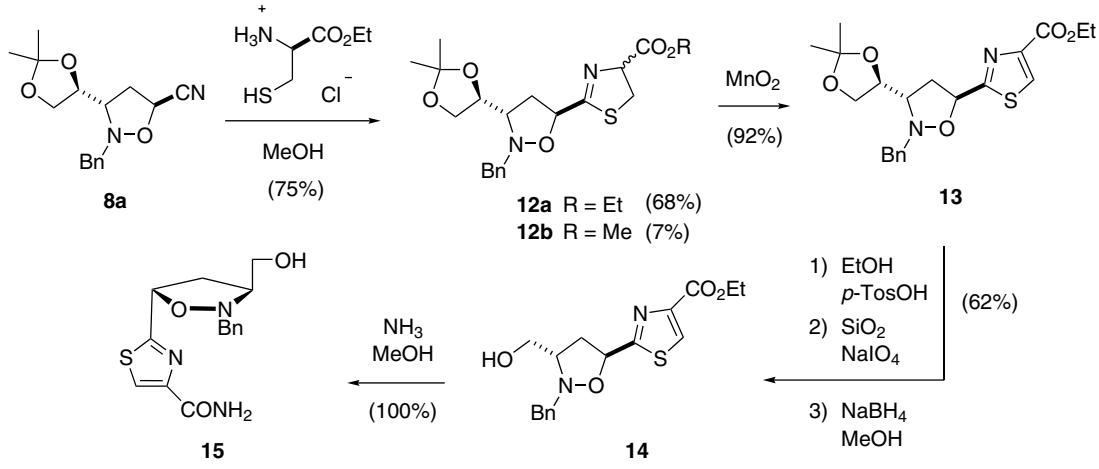


Scheme 3. Synthesis of isoxazolidinyl analogue of tiazofurin **5**.

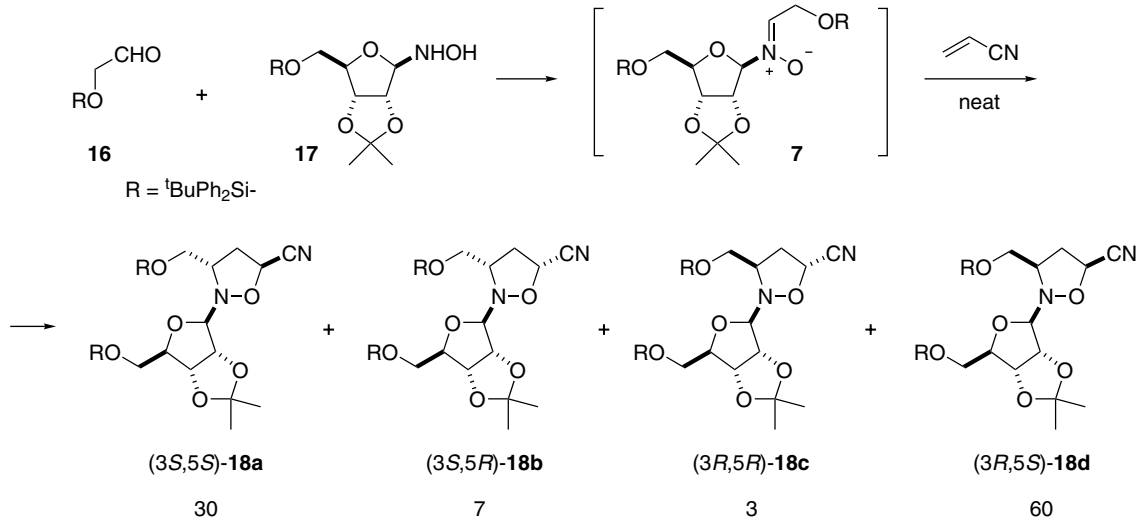
of tiazofurin **15** (Scheme 4). The reaction of **8a** with L-cysteine afforded a ca. 10:1 mixture of thiazolines **12a** and **12b**, from which the major compound **12a** was separated as a mixture of epimers. Oxidation of pure **12a** gave rise to thiazole **13** in 90% yield. Acidic hydrolysis of **13**, followed by oxidation with the heterogeneous system[24] $NaIO_4$–SiO_2 and further reduction of the emerging aldehyde with $NaBH_4$ provided **14**, the ammonolysis of which furnished *trans*-isoxazolidinyl tiazofurin **15**; overall yield based on **6**: 39% (seven steps).

2.2. Synthesis from *N*-(D-ribosyl)-*C*-(*tert*-butyldiphenylsiloxymethyl) nitrone 7

Our second approach to isoxazolidinyl tiazofurin consisted of using the *N*-ribosyl nitrone **7** as starting material in which the carbohydrate unit acted both as a chiral auxiliary and as a protecting group. (Scheme 1). Nitrone **7** was prepared in situ from the condensation of aldehyde **16**, obtained from (±)-solketal,[25] with an equimolar amount of hydroxylamine **17** obtained from D-ribose.[26]



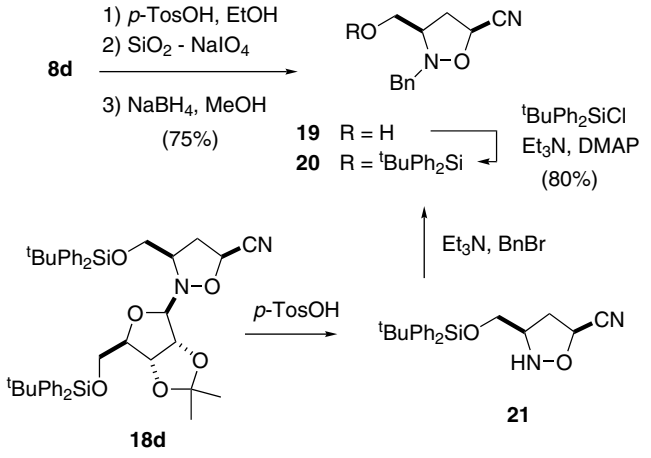
Scheme 4. Synthesis of the *trans*-isoxazolidinyl analogue of tiazofurin **15**.



Scheme 5. Cycloaddition between **7** and acrylonitrile.

Thus, the cycloaddition reaction was carried out by heating at 70 °C for 12 h in a sealed tube solution of **16** and **17** in acrylonitrile and in the absence of a solvent (Scheme 5). NMR analysis of the crude mixture showed the presence of four adducts in a isomeric ratio of ca. 60:30:7:3, which were obtained in a combined yield of 86%. The crude mixture was purified by MPLC (hexane/diethyl ether, 3:2 as eluant) and the major adduct **18d** obtained in pure form (we were unable to separate completely minor isomers by MPLC or HPLC and only enriched compounds were isolated: see Section 4).

The stereochemical assignment of the major adduct **18d** was made by chemical correlation by comparison of a further derivative with the same compound obtained from the above described **8d** (Scheme 6).



Scheme 6. Determination of the configuration of **18d**.

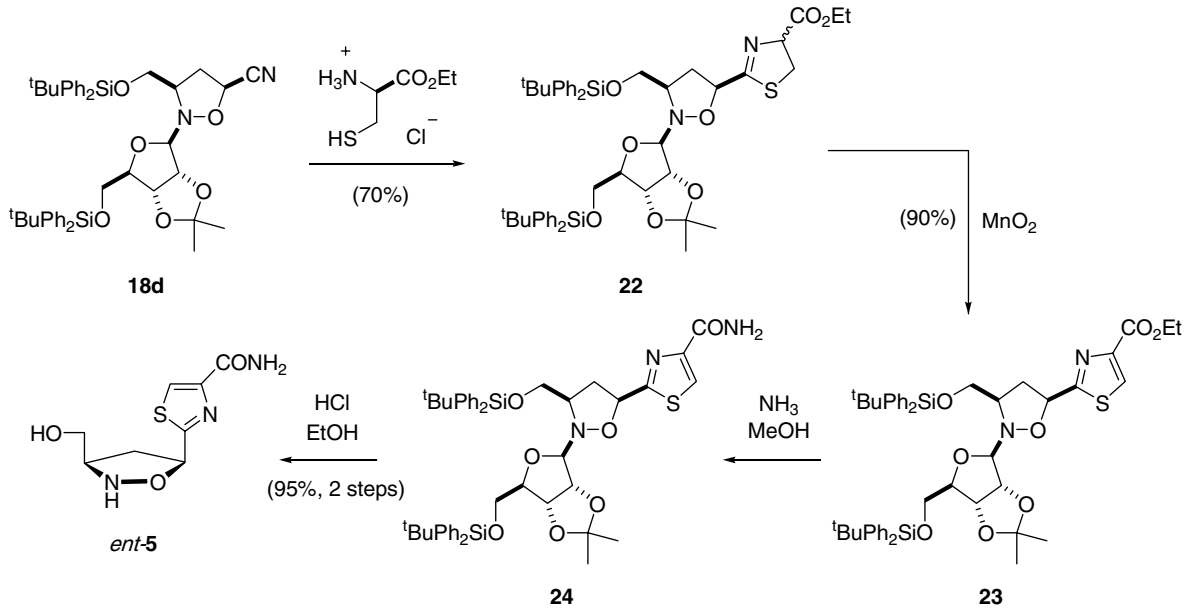
Compound **18d** was converted into **21** by acidic treatment (*p*-toluenesulfonic acid in methanol), which was subsequently N-benzylated to give isoxazolidine **20**. This compound was also obtained from **8d** through the transformation of the dioxolane ring into a hydroxymethyl group and silylated under usual conditions.[23] Both products showed identical physical and spectroscopic properties including the sign of specific rotation, demonstrating unambiguously the (3*R*,5*S*)-configuration of compound **18d**.[27]

Analogous to the results described above, condensation of adduct **18d** with L-cysteine in dry methanol[22] provided thiazoline **22** in good yield as a mixture of epimers (less than 3% of transesterification was observed). The thiazoline ring was oxidized (MnO_2) and the resulting isoxazolidinyl thiazole **23** treated with ammonia in methanol to afford **24**, which was in situ transformed by acidic treatment (1.5% HCl in EtOH) into isoxazolidinyl tiazofurin *ent*-**5** (60% overall yield; four steps) (Scheme 7).

3. Conclusions

In conclusion, the approach described herein for the preparation of new nucleoside analogues of tiazofurin combines the stereochemical preference of the cycloaddition reaction between nitrones **6** and **7**, and acrylonitrile and efficiency in constructing the thiazole ring. Remarkably, a complementary selectivity between nitrones **6** and **7** has been observed, leading to the preparation of enantiomeric analogues **5** and *ent*-**5** other key steps are the transformation of the dioxolane ring into the hydroxymethyl group and the use of a chiral auxiliary that can be easily removed to afford isoxazolidinyl analogue *ent*-**5**, unsubstituted on the nitrogen atom. In the case of analogue **5**, the *N*-benzyl group proved to be difficult to eliminate due to the incompatibility of reductive methods with both the N–O bond and the thiazole moiety.[28] In this respect, the methodology based on *N*-glycosyl nitrone **7** is more advantageous, since allows preparation of unprotected analogues.[29]

Since the cyano group is the starting point for the construction of a variety of heterocyclic systems, our approach can also be used for incorporating other heterocyclic bases with a *cis*-configuration with respect



Scheme 7. Synthesis of isoxazolidinyl tiazofurin *ent*-**5**.

to the hydroxymethyl group as preferred in nucleoside analogues. The extension of the methodology towards the preparation of other optically active isoxazolidinyl-*C*-nucleosides is currently underway.

4. Experimental

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA) and with solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL/min. Column chromatography was carried out in a Buchi 800 MPLC system using silica gel SDS 5–60 μm. Analytical HPLC was carried out in a Waters Alliance system with RI and PDA detection. Semi-preparative HPLC was performed using C18 reverse phase columns at a maximum flow of 25 mL/min with a Waters isocratic pump. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 or Varian 500 instruments in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta = 7.26$) in $CDCl_3$. Optical rotations were taken at 25 °C on a Perkin–Elmer 241 polarimeter. Elemental analyses were performed on a Perkin–Elmer 240B microanalyzer. Nitrone **6** was prepared from D-glyceraldehyde as described.[30]

4.1. 1,3-Dipolar cycloaddition of nitrone 6 with acrylonitrile

Nitrone **6** (1.88 g, 8 mmol) was dissolved in acrylonitrile (17 g, 0.32 mol) and the resulting solution stirred at reflux until no more nitrone was observed (TLC, ca. 4 h). The reaction mixture was evaporated to dryness and the residue was analyzed by NMR to determine the diastereomeric ratio. Purification by radial chromatography (hexane/EtOAc, 80:20) and semipreparative HPLC (hexane/^{i}PrOH, 98:2) gave the pure adducts.

4.1.1. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-cyanoisoxazolidine 8a. Eluted first (0.807 g, 35%), oil; $[\alpha]_D = +43$ (*c* 0.22, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.27 (s, 3H), 1.32 (s, 3H), 2.87 (dd, 1H, $J = 5.2$, 7.3 Hz), 3.39 (dt, 1H, $J = 4.4$, 8.8 Hz), 3.48 (dd, 1H, $J = 5.2$, 8.8 Hz), 3.85 (dt, 1H, $J = 5.1$, 8.1 Hz), 3.91 (d, 1H, $J = 13.2$ Hz), 3.99 (dd, 1H, $J = 5.9$, 8.8 Hz), 4.10 (pseudo q, 1H, $J = 7.3$ Hz), 4.30 (d, 1H, $J = 13.2$ Hz), 4.75 (dd, 1H, $J = 7.3$, 8.1 Hz), 7.33 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.0, 26.8, 36.1, 62.0, 64.8, 67.5, 67.9, 75.8, 109.6, 119.8, 128.0, 128.6 (2C), 129.3 (2C), 135.9. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.80; H, 7.11; N, 9.64.

4.1.2. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-cyanoisoxazolidine 8b. Eluted second (1.15 g, 50%), white solid; mp 71–73 °C; $[\alpha]_D = -50$ (*c* 0.27, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.32 (s, 3H), 1.36 (s, 3H), 2.65 (dd, 1H, $J = 4.1$, 13.2 Hz), 2.78 (dt, 1H, $J = 8.8$, 13.2 Hz), 3.22 (dt, 1H, $J = 4.1$, 8.0 Hz), 3.65 (dd, 1H, $J = 5.5$, 8.5 Hz), 3.95 (s, 2H), 4.05 (dd, 1H, $J = 6.3$, 8.5 Hz), 4.17 (dt, 1H, $J = 5.9$, 7.7 Hz), 4.84 (dd, 1H, $J = 4.4$, 9.0 Hz), 7.32 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.1, 26.7, 36.4, 61.3, 64.2, 66.3, 67.4, 75.5, 109.7, 118.0, 128.0, 128.6 (2C), 128.9 (2C),

135.7. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.73, H, 6.80, N, 9.91.

4.1.3. (3*R*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-cyanoisoxazolidine 8c. Eluted third (0.231 g, 10%), sticky foam; $[\alpha]_D = +11$ (*c* 0.37, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.30 (s, 3H), 1.37 (s, 3H), 2.52 (ddd, 1H, $J = 5.9$, 8.8, 13.2 Hz), 2.75 (ddd, 1H, $J = 4.4$, 8.1, 13.2 Hz), 3.50 (pseudo q, 1H, $J = 5.9$ Hz), 3.69 (dd, 1H, $J = 5.9$, 8.8 Hz), 3.94 (dd, 1H, $J = 6.6$, 8.1 Hz), 4.07 (pseudo q, 1H, $J = 5.9$ Hz), 4.19 (d, 1H, $J = 13.2$ Hz), 4.28 (d, 1H, $J = 13.2$ Hz), 4.70 (dd, 1H, $J = 4.4$, 8.8 Hz), 7.32 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.5, 26.5, 36.9, 61.5, 64.6, 66.9, 67.3, 76.1, 110.3, 118.9, 127.9, 128.7 (2C), 129.0 (2C), 136.1. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.41; H, 6.84; N, 9.83.

4.1.4. (3*R*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-cyanoisoxazolidine 8d. Eluted fourth (0.115 g, 5%), white solid; mp 115–117 °C; $[\alpha]_D = -32$ (*c* 0.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.34 (s, 3H), 1.43 (s, 3H), 2.29 (ddd, 1H, $J = 3.5$, 7.0, 13.1 Hz), 2.70 (dt, 1H, $J = 9.2$, 13.1 Hz), 3.05 (pseudo q, 1H, $J = 7.4$ Hz), 3.79 (dd, 1H, $J = 7.4$, 9.3 Hz), 3.95 (d, 1H, $J = 15.0$ Hz), 4.09 (dd, 1H, $J = 7.6$, 9.4 Hz), 4.26 (pseudo q, 1H, $J = 6.7$ Hz), 4.50 (d, 1H, $J = 15.0$ Hz), 4.73 (dd, 1H, $J = 3.5$, 9.0 Hz), 7.38 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.4, 26.9, 37.7, 60.9, 63.9, 66.5, 66.9, 76.6, 110.5, 119.0, 127.7, 128.6 (2C), 128.8 (2C), 136.7. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.80, H, 6.73, N, 9.59.

4.2. Condensation between 8b and L-cysteine

To a well-stirred solution of **8b** (0.865 g, 3 mmol) in dry methanol (50 mL) at room temperature under an argon atmosphere was added (*S*)-cysteine ethyl ester hydrochloride (0.835 g, 4.5 mmol) and triethylamine (0.455 g, 4.5 mmol). The resulting mixture was stirred for 3 h and evaporated to dryness. The residue was taken up in CH_2Cl_2 and washed with water, 5% $NaHCO_3$ solution and brine. The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product, containing 6% of the corresponding methyl ester, can be used as such for the next reaction. It can also be purified by radial chromatography (hexane/EtOAc, 90:10) to give pure products.

4.2.1. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[(4*RS*)-4-(ethoxycarbonyl)-2-thiazolin-2-yl]-isoxazolidine 9a (mixture of epimers). 0.883 g (70%), oil; δ_H (400 MHz, $CDCl_3$): 1.27 (s, 3H), 1.28 (t, 3H, $J = 7.0$ Hz), 1.29 (s, 3H), 2.50 (ddt, 1H, $J = 3.3$, 6.3, 13.2 Hz), 2.86 (ddt, 1H, $J = 5.3$, 8.8, 13.2 Hz), 3.19 (ddt, 1H, $J = 3.3$, 7.0, 8.1 Hz), 3.40–3.50 (m, 3H), 3.82 (d, 1H, $J = 12.9$ Hz), 3.95 (dd, 1H, $J = 5.9$, 9.1 Hz), 4.02 (d, 1H, $J = 12.9$ Hz), 4.11 (dt, 1H, $J = 5.9$, 9.1 Hz), 4.22 (dq, 2H, $J = 1.8$, 7.0 Hz), 5.06 (dt, 1H, $J = 7.0$, 9.1 Hz), 5.18 (ddt, 1H, $J = 3.5$, 6.3, 8.8 Hz), 7.26–7.32 (m, 5H); δ_C (100 MHz, $CDCl_3$): 14.2, 25.3, 26.9, 34.2, 34.5, 37.2, 61.5, 61.8, 66.5, 66.8, 67.8, 77.9, 109.2, 127.8, 128.5 (2C), 129.3 (2C), 136.2, 170.5, 176.4.

4.2.2. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[(4*S*)-4-(methoxycarbonyl)-2-thiazolin-2-yl]-isoxazolidine 9b. 76 mg (6%), oil; $[\alpha]_D = -4$ (*c* 0.10, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.28 (s, 3H), 1.30 (s, 3H), 2.50 (dddd, 1H, $J = 4.1$, 6.5, 7.6, 13.0 Hz), 2.88 (ddt, 1H, $J = 3.5$, 8.8, 13.0 Hz), 3.20 (ddt, 1H, $J = 3.5$, 7.0, 8.2 Hz), 3.40–3.56 (m, 3H), 3.79 (s, 3H), 3.83 (d, 1H, $J = 12.9$ Hz), 3.90 (ddd, 1H, $J = 3.5$, 6.5, 9.4 Hz), 4.10 (d, 1H, $J = 12.9$ Hz), 4.16 (dt, 1H, $J = 5.9$, 8.2 Hz), 5.08 (dt, 1H, $J = 4.7$, 9.4 Hz), 5.17 (ddd, 1H, $J = 3.5$, 5.8, 9.4 Hz), 7.30–7.38 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.2, 26.8, 34.1, 34.4, 37.2, 52.8, 61.5, 66.6, 66.8, 67.8, 77.9, 109.2, 127.8, 128.5 (2C), 129.3 (2C), 136.2, 171.0, 176.5. Anal. Calcd for $C_{20}H_{26}N_2O_5S$ (406.50): C, 59.09; H, 6.45; N, 6.89. Found: C, 59.25; H, 6.27; N, 7.02.

4.3. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[4-(ethoxycarbonyl)-2-thiazolyl]isoxazolidine 10a

To a well-stirred solution of **9a** (0.841 g, 2 mmol) in benzene (40 mL) at room temperature was added activated MnO_2 (2.0 g). The resulting suspension was refluxed for 12 h and then filtered. The solid was washed with CH_2Cl_2 and the filtrate evaporated to dryness. The crude product was purified by radial chromatography (hexane/EtOAc, 85:15) to afford 0.753 g (90%) of pure **10a** as an oil. $[\alpha]_D = -16$ (*c* 0.39, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.20 (s, 3H), 1.23 (s, 3H), 1.33 (t, 3H, $J = 7.0$ Hz), 2.48 (ddd, 1H, $J = 4.0$, 5.8, 13.4 Hz), 3.00 (dt, 1H, $J = 8.8$, 13.4 Hz), 3.24 (ddd, 1H, $J = 4.0$, 7.6, 8.8 Hz), 3.47 (dd, 1H, $J = 5.8$, 8.3 Hz), 3.93 (dd, 1H, $J = 6.3$, 8.3 Hz), 3.94 (d, 1H, $J = 13.2$ Hz), 4.04 (q, 1H, $J = 6.2$ Hz), 4.05 (d, 1H, $J = 13.2$ Hz), 4.35 (q, 2H, $J = 7.0$ Hz), 5.56 (dd, 1H, $J = 5.8$, 9.1 Hz), 7.22–7.34 (m, 5H), 8.05 (s, 1H); δ_C (100 MHz, $CDCl_3$): 14.3, 25.1, 26.6, 38.7, 61.4, 61.7, 67.1, 67.5, 76.8, 78.0, 109.3, 127.8, 127.9, 128.5 (2C), 129.3 (2C), 136.2, 146.9, 161.3, 172.6. Anal. Calcd for $C_{21}H_{26}N_2O_5S$ (418.51): C, 60.27; H, 6.26; N, 6.69. Found: C, 60.09; H, 6.17; N, 6.81.

4.4. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[4-(methoxycarbonyl)-2-thiazolyl]isoxazolidine 10b

Treatment of **9b** (80 mg, 0.2 mmol) under the same conditions described above for the preparation of **10a** provided after radial chromatography (hexane/EtOAc, 85:15) 71 mg (88%) of pure **10b** as an oil $[\alpha]_D = -23$ (*c* 0.12, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.20 (s, 3H), 1.23 (s, 3H), 2.48 (ddd, 1H, $J = 4.0$, 5.6, 13.2 Hz), 3.02 (dt, 1H, $J = 8.8$, 13.2 Hz), 3.24 (ddd, 1H, $J = 4.0$, 7.6, 8.8 Hz), 3.47 (dd, 1H, $J = 5.6$, 8.3 Hz), 3.90 (dd, 1H, $J = 6.3$, 8.3 Hz), 3.94 (d, 1H, $J = 13.2$ Hz), 3.99 (s, 3H), 4.06 (m, 1H), 4.05 (d, 1H, $J = 13.2$ Hz), 5.56 (dd, 1H, $J = 5.8$, 9.1 Hz), 7.22–7.34 (m, 5H), 8.05 (s, 1H); δ_C (100 MHz, $CDCl_3$): 25.1, 26.6, 38.8, 61.3, 61.7, 67.4 (2C), 76.6, 77.6, 109.3, 127.8, 127.9, 128.5 (2C), 129.3 (2C), 136.2, 146.9,

161.4, 173.0. Anal. Calcd for $C_{20}H_{24}N_2O_5S$ (404.48): C, 59.39; H, 5.98; N, 6.93. Found: C, 59.48; H, 5.80; N, 7.02.

4.5. (3*S*,5*R*)-2-Benzyl-3-(hydroxymethyl)-5-[4-(ethoxycarbonyl)-2-thiazolyl]isoxazolidine 11a

To a solution of **10a** (0.7 g, 1.67 mmol) in EtOH (50 mL) was added *p*-toluenesulfonic acid (86 mg, 0.5 mmol) and the resulting mixture heated at 60 °C for 4 h, at which time the reaction mixture was treated with saturated aq $NaHCO_3$ (50 mL) and partially evaporated under reduced pressure. The residue was taken up in EtOAc (50 mL) and washed with brine. The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude diol was dissolved in CH_2Cl_2 (5 mL) and added to a vigorously stirred suspension previously formed with chromatographic grade silica gel (3.3 g), 0.65 M aq solution of $NaIO_4$ (3.3 mL), and CH_2Cl_2 (25 mL). The reaction mixture was stirred for 15 min and filtered. The silica gel was washed with CH_2Cl_2 (2×15 mL) and the filtrate evaporated under reduced pressure to dryness. The crude aldehyde was then dissolved in MeOH (20 mL), cooled to 0 °C and treated with $NaBH_4$ (113 mg, 3 mmol). After stirring at 0 °C for 1 h the reaction mixture is treated with saturated aq $NaHCO_3$ (50 mL) and partially evaporated under reduced pressure. The residue was taken up in EtOAc (40 mL) and washed with brine. The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by radial chromatography (hexane/EtOAc, 75:25) to afford 0.431 g (74%) of pure **11a** as an oil; $[\alpha]_D = -2$ (*c* 0.55, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.32 (t, 3H, $J = 7.0$ Hz), 2.08 (dd, 1H, $J = 5.6$, 6.6 Hz, ex. D_2O), 2.26 (dt, 1H, $J = 5.1$, 13.2 Hz), 2.95 (dt, 1H, $J = 8.8$, 13.2 Hz), 3.31 (ddt, 1H, $J = 4.5$, 7.3, 8.8 Hz), 3.42 (ddd, 1H, $J = 4.3$, 6.6, 11.4 Hz), 3.46 (ddd, 1H, $J = 5.6$, 7.3, 11.4 Hz), 3.96 (d, 1H, $J = 13.2$ Hz), 4.07 (d, 1H, $J = 13.2$ Hz), 4.35 (q, 2H, $J = 7.0$ Hz), 5.50 (dd, 1H, $J = 5.6$, 9.1 Hz), 7.28–7.39 (m, 5H), 8.04 (s, 1H); δ_C (100 MHz, $CDCl_3$): 14.4, 38.4, 61.4, 61.5, 62.9, 66.8, 76.4, 127.8, 127.9, 128.6 (2C), 129.2 (2C), 136.3, 146.9, 161.3, 172.9. Anal. Calcd for $C_{17}H_{20}N_2O_4S$ (348.42): C, 58.60; H, 5.79; N, 8.04. Found: C, 58.86; H, 5.61; N, 8.29.

4.6. (3*S*,5*R*)-2-Benzyl-3-(hydroxymethyl)-5-[4-(methoxycarbonyl)-2-thiazolyl]isoxazolidine 11b

Treatment of **10b** (60 mg, 0.15 mmol) under the same conditions described above for the preparation of **11a** provided after radial chromatography (hexane/EtOAc, 75:25) 40 mg (80%) of pure **11b** as an oil. $[\alpha]_D = -11$ (*c* 0.21, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.10 (br s, 1H), 2.25 (dt, 1H, $J = 5.1$, 13.2 Hz), 2.95 (dt, 1H, $J = 8.7$, 13.2 Hz), 3.31 (ddt, 1H, $J = 4.4$, 7.3, 8.7 Hz), 3.42–3.48 (m, 2H), 3.86 (s, 3H), 3.98 (d, 1H, $J = 13.0$ Hz), 4.06 (d, 1H, $J = 13.0$ Hz), 5.50 (dd, 1H, $J = 5.6$, 9.0 Hz), 7.28–7.39 (m, 5H), 8.06 (s, 1H); δ_C (100 MHz, $CDCl_3$): 38.4, 61.5, 61.5, 62.9, 66.9, 76.3, 127.8, 127.9, 128.6 (2C), 129.2 (2C), 136.3, 146.8, 161.7, 172.6. Anal. Calcd for $C_{16}H_{18}N_2O_4S$ (334.39): C, 57.47; H, 5.43; N, 8.38. Found: C, 57.44; H, 5.32; N, 8.57.

4.7. (3*S*,5*R*)-2-Benzyl-3-(hydroxymethyl)-5-[4-(aminocarbonyl)-2-thiazolyl]isoxazolidine 5

Ammonia gas was bubbled through a well stirred solution of **10** (0.4 g, 1.15 mmol) in MeOH (15 mL) at room temperature. After 1 h, the reaction mixture was evaporated under reduced pressure to dryness. The residue was purified by radial chromatography (hexane/EtOAc, 65:35) to give 0.367 g (100%) of pure **5** as an oil. $[\alpha]_D = -28$ (*c* 0.20, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.35 (br t, 1H, $J = 5.8$ Hz, ex. D_2O), 2.42 (dt, 1H, $J = 5.1$, 12.9 Hz), 3.00 (dt, 1H, $J = 8.8$, 12.9 Hz), 3.40 (ddd, 1H, $J = 4.3$, 8.8, 12.4 Hz), 3.50–3.61 (m, 2H), 4.11 (d, 1H, $J = 13.3$ Hz), 4.20 (d, 1H, $J = 13.3$ Hz), 5.49 (dd, 1H, $J = 5.6$, 8.8 Hz), 5.92 (br s, 1H, ex. D_2O), 7.10 (br s, 1H, ex. D_2O), 7.32–7.41 (m, 5H), 8.10 (s, 1H); δ_C (100 MHz, $CDCl_3$): 38.0, 61.3, 62.8, 66.8, 76.0, 124.9, 127.8, 128.6 (2C), 129.1 (2C), 136.3, 149.2, 162.8, 172.0. Anal. Calcd for $C_{15}H_{17}N_3O_3S$ (319.38): C, 56.41; H, 5.37; N, 13.16. Found: C 56.29, H, 5.56, N, 12.96.

Application of these conditions to compound **11b** also afforded pure **5** quantitatively.

4.8. Condensation between 8a and L-cysteine

Treatment of **8a** (0.865 g, 3 mmol) under the conditions described above for the preparation of **9** gave a crude product containing 7% of the corresponding methyl ester. Pure compounds were obtained after radial chromatography (hexane/EtOAc, 90:10).

4.8.1. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[(4*RS*)-4-(ethoxycarbonyl)-2-thiazolin-2-yl]-isoxazolidine 12a (mixture of epimers). 0.858 g (68%); oil; δ_H (400 MHz, $CDCl_3$): 1.23 (s, 3H), 1.25 (t, 3H, $J = 7.0$ Hz), 1.26 (s, 3H), 2.65–2.75 (m, 2H), 3.19 (ddd, 1H, $J = 5.1$, 6.4, 10.3 Hz), 3.40–3.55 (m, 3H), 3.78 (d, 1H, $J = 12.9$ Hz), 3.85 (d, 1H, $J = 12.9$ Hz), 3.90–3.96 (m, 2H), 4.19 (q, 2H, $J = 7.0$ Hz), 4.89 (q, 1H, $J = 8.0$ Hz), 5.08 (ddt, 1H, $J = 1.26$, 7.3, 9.6 Hz), 7.23–7.31 (m, 5H); δ_C (100 MHz, $CDCl_3$): 14.2, 25.2, 26.7, 35.0, 35.1, 35.4, 61.8, 61.9, 66.8, 66.9, 67.7, 78.1, 109.4, 127.7, 128.8 (2C), 129.3 (2C), 136.8, 170.5, 177.1.

4.8.2. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[(4*S*)-4-(methoxycarbonyl)-2-thiazolin-2-yl]-isoxazolidine 12b. 85 mg (7%), oil; $[\alpha]_D = -18$ (*c* 0.10, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.23 (s, 3H), 1.26 (s, 3H), 2.65 (dt, 1H, $J = 7.6$, 12.9 Hz), 2.74 (ddd, 1H, $J = 3.0$, 8.0, 12.9 Hz), 3.19 (dt, 1H, $J = 3.0$, 7.6 Hz), 3.39–3.46 (m, 2H), 3.54 (dd, 1H, $J = 9.1$, 11.1 Hz), 3.74 (s, 3H), 3.80 (d, 1H, $J = 12.9$ Hz), 3.90–3.97 (m, 2H), 4.15 (d, 1H, $J = 12.9$ Hz), 4.90 (q, 1H, $J = 8.1$ Hz), 5.08 (ddt, 1H, $J = 1.3$, 5.9, 9.3 Hz), 7.28–7.33 (m, 5H); δ_C (100 MHz, $CDCl_3$): 25.2, 26.8, 34.8, 35.0, 35.6, 52.8, 63.04, 66.8, 66.9, 67.8, 78.2, 109.5, 127.7, 128.5 (2C), 129.3 (2C), 136.7, 171.0, 177.4. Anal. Calcd for $C_{20}H_{26}N_2O_5S$ (406.50): C, 59.09; H, 6.45; N, 6.89. Found: C, 58.84; H, 6.51; N, 7.11.

4.9. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-[4-(ethoxycarbonyl)-2-thiazolyl]isoxazolidine 13

Treatment of **12a** (0.841 g, 2 mmol) under the conditions described above for the preparation of **10a** gave after radial chromatography (hexane/EtOAc, 85:15) 0.77 g (92%) of pure **13** as an oil. $[\alpha]_D = -3$ (*c* 0.68, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.26 (s, 3H), 1.30 (s, 3H), 1.34 (t, 3H, $J = 7.0$ Hz), 2.72 (dt, 1H, $J = 7.6$, 12.9 Hz), 2.94 (ddd, 1H, $J = 3.3$, 8.1, 12.9 Hz), 3.29 (dt, 1H, $J = 3.3$, 7.3 Hz), 3.50 (dd, 1H, $J = 5.8$, 8.3 Hz), 3.87 (d, 1H, $J = 12.9$ Hz), 3.98 (dd, 1H, $J = 6.1$, 8.1 Hz), 4.06 (q, 1H, $J = 6.1$ Hz), 4.12 (d, 1H, $J = 12.9$ Hz), 4.39 (q, 2H, $J = 7.0$ Hz), 5.39 (t, 1H, $J = 7.8$ Hz), 7.28–7.33 (m, 5H), 8.1 (s, 1H); δ_C (100 MHz, $CDCl_3$): 14.4, 25.1, 26.8, 37.1, 60.4, 61.5, 67.0, 67.7, 75.4, 78.1, 109.5, 127.7, 127.8, 128.5 (2C), 129.2 (2C), 136.6, 147.8, 161.3, 173.3. Anal. Calcd for $C_{21}H_{26}N_2O_5S$ (418.51): C, 60.27; H, 6.26; N, 6.69. Found: C, 60.09; H, 6.17; N, 6.81.

4.10. (3*S*,5*S*)-2-Benzyl-3-(hydroxymethyl)-5-[4-(ethoxycarbonyl)-2-thiazolyl]isoxazolidine 14

Treatment of **13** (0.7 g, 1.67 mmol) under the conditions described above for the preparation of **11a** gave after radial chromatography (hexane/EtOAc, 75:25) 0.361 g (62%) of pure **14** as an oil. $[\alpha]_D = -29$ (*c* 0.65, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.38 (t, 3H, $J = 7.0$ Hz), 2.01 (br d, 1H, $J = 6.0$ Hz, ex. D_2O), 2.39 (m, 1H), 2.75 (m, 1H), 3.37 (quintuplet, 1H, $J = 5.9$ Hz), 3.54–3.60 (m, 2H), 4.01 (d, 1H, $J = 13.2$ Hz), 4.17 (d, 1H, $J = 13.2$ Hz), 4.39 (q, 2H, $J = 7.0$ Hz), 5.38 (t, 1H, $J = 7.4$ Hz), 7.24–7.36 (m, 5H), 8.13 (s, 1H); δ_C (100 MHz, $CDCl_3$): 14.4, 38.0, 61.5, 62.2, 62.6, 66.0, 77.5, 127.7, 127.8, 128.5 (2C), 129.1 (2C), 136.5, 147.2, 161.3, 173.3. Anal. Calcd for $C_{17}H_{20}N_2O_4S$ (348.42): C, 58.60; H, 5.79; N, 8.04. Found: C, 58.55; H, 5.69; N, 7.98.

4.11. (3*S*,5*S*)-2-Benzyl-3-(hydroxymethyl)-5-[4-(aminocarbonyl)-2-thiazolyl]isoxazolidine 15

Treatment of **14** (0.3 g, 0.86 mmol) under the conditions described above for the preparation of **5a** gave after radial chromatography (hexane/EtOAc, 65:35) 0.275 g (100%) of pure **15** as an oil. $[\alpha]_D = -44$ (*c* 0.40, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.41 (br t, 1H, $J = 5.9$ Hz, ex. D_2O), 2.74 (dt, 1H, $J = 5.6$, 12.9 Hz), 2.80 (dt, 1H, $J = 7.0$, 12.9 Hz), 3.45 (dt, 1H, $J = 5.5$, 11 Hz), 3.61–3.66 (m, 2H), 4.05 (d, 1H, $J = 13.3$ Hz), 4.21 (d, 1H, $J = 13.3$ Hz), 5.34 (t, 1H, $J = 7.4$ Hz), 5.91 (br s, 1H, ex. D_2O), 7.10 (br s, 1H, ex. D_2O), 7.30–7.39 (m, 5H), 8.16 (s, 1H); δ_C (100 MHz, $CDCl_3$): 37.8, 62.4, 62.8, 66.2, 77.2, 124.8, 127.7, 128.5 (2C), 129.1 (2C), 136.6, 149.4, 162.8, 172.1. Anal. Calcd for $C_{15}H_{17}N_3O_3S$ (319.38): C, 56.41; H, 5.37; N, 13.16. Found: C, 56.60; H, 5.49; N, 13.30.

4.12. 1,3-Dipolar cycloaddition of nitrone 7 with acrylonitrile

A solution of aldehyde **16**[25] (1.48 g, 4.94 mmol), hydroxylamine **17**[26] (2.12 g, 4.94 mmol), and acrylonitrile (15 mL, 234.5 mmol) was heated at 70 °C, in a sealed tube, for 12 h. The reaction mixture was evaporated and the residue purified by MPLC chromatography (hexane/EtOAc, 95:5) and then by semi-preparative HPLC (hexane/^{i}PrOH, 99:1). Only major compound **18d** was completely separated and fully characterized, the minor adducts **18a** and **18b** containing minor amounts (<5%) of other isomers.

4.12.1. (3*S*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(*tert*-butyldiphenylsiloxymethyl)-5-cyanoisoxazolidine 18a.

δ_H (300 MHz, $CDCl_3$): 1.01 (s, 18H), 1.3 (s, 3H), 1.5 (s, 3H), 2.61 (ddd, 1H, $J = 3.4$, 4.9, 9.5 Hz), 3.35 (ddd, 1H, $J = 3.2$, 4.9, 9.5 Hz), 3.54 (m, 2H), 3.80 (m, 1H), 4.10 (m, 3H), 4.45 (t, 1H, $J = 4.9$ Hz), 4.62 (m, 2H), 4.8 (d, 1H, $J = 0.7$ Hz), 7.20–7.34 (m, 12H), 7.45–7.60 (m, 8H); δ_C (75 MHz, $CDCl_3$): 19.2, 25.3, 26.6, 36.7, 61.5, 63.1, 64.7, 64.8, 80.4, 82.6, 83.4, 86.0, 112.6, 118.3, 127.4, 129.8, 129.6, 133.2, 134.7, 135.3, 135.5. Anal. Calcd for $C_{45}H_{56}N_2O_6Si_2$ (777.11): C, 69.55; H, 7.26; N, 3.60. Found: C, 69.60; H, 7.30; N, 3.75.

4.12.2. (3*S*,5*R*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(*tert*-butyldiphenylsiloxymethyl)-5-cyanoisoxazolidine 18b.

δ_H (500 MHz, $CDCl_3$): 1.03 (s, 18H), 1.31 (s, 3H), 1.45 (s, 3H), 2.34 (dt, 1H, $J = 4.5$, 9.5 Hz), 2.53 (ddd, 1H, $J = 3.0$, 4.0, 9.5 Hz), 3.59 (dd, 1H, $J = 10.5$, 4.9 Hz), 3.65 (dd, 1H, $J = 6.5$, 10.5 Hz), 3.75 (m, 2H), 4.10 (dd, 1H, $J = 5.5$, 8.0 Hz), 4.47 (dd, 1H, $J = 4.5$, 9.0 Hz), 4.51 (dd, 1H, $J = 4.0$. 9.0 Hz), 4.71 (dddd, 1H, $J = 4.0$, 4.5, 4.9, 6.5 Hz), 4.79 (dd, 1H, $J = 3.0$. 4.5 Hz), 4.82 (d, 1H, $J = 2.5$ Hz), 7.24–7.34 (m, 12H), 7.50–7.65 (m, 8H); δ_C (125 MHz, $CDCl_3$): 19.2, 25.2, 26.5, 36.8, 61.5, 63.2, 64.6, 64.9, 80.4, 82.6, 83.4, 85.9, 112.6, 118.4, 127.4, 129.8, 129.9, 133.1, 134.7, 135.4, 135.5. Anal. Calcd for $C_{45}H_{56}N_2O_6Si_2$ (777.11): C, 69.55; H, 7.26; N, 3.60. Found: C, 69.68; H, 7.34; N, 3.80.

4.12.3. (3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(*tert*-butyldiphenylsiloxymethyl)-5-cyanoisoxazolidine 18d.

$[\alpha]_D = -7$ (*c* 0.62, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$): 1.02 (s, 18H), 1.26 (s, 3H), 1.46 (s, 3H), 2.45 (ddd, 1H, $J = 3.0$, 5.9, 12.7 Hz), 2.64 (ddd, 1H, $J = 7.8$, 8.9, 12.7 Hz), 3.56 (dd, 1H, $J = 4.6$, 10.8 Hz), 3.65 (dd, 1H, $J = 10.8$, 6.2 Hz), 4.49 (dddd, 1H, $J = 3.0$, 4.6, 6.2, 7.8 Hz), 4.51 (dd, 1H, $J = 3.1$, 6.8 Hz), 4.58 (dd, 1H, $J = 3.1$, 6.8 Hz), 4.65 (t, 1H, $J = 1.7$ Hz), 4.70 (d, 1H, $J = 1.7$ Hz), 4.71 (d, 1H, $J = 3.1$ Hz), 4.80 (dd, 1H, $J = 5.9$, 8.9 Hz), 4.82 (d, 1H, $J = 1.7$ Hz), 7.22–7.36 (m, 12H), 7.53–7.62 (m, 8H); δ_C (125 MHz, $CDCl_3$): 19.15, 25.11, 26.52, 36.84, 61.59, 63.58, 64.65, 65.66, 80.22, 82.70, 83.42, 85.09, 113.69, 118.40, 127.69, 129.80, 129.89, 132.95, 134.77, 135.42, 135.51. Anal. Calcd for $C_{45}H_{56}N_2O_6Si_2$ (777.11): C, 69.55; H, 7.26; N, 3.60. Found: C, 69.71; H, 7.39; N, 3.83.

4.13. (3*R*,5*S*)-2-Benzyl-3-(hydroxymethyl)-5-cyanoisoxazolidine 19

Treatment of **8d** (0.1 g, 0.35 mmol) under the conditions described above for the preparation of **11a** afforded after

radial chromatography (hexane/EtOAc, 80:20) 57 mg (75%) of pure **19** as a foam. $[\alpha]_D = +76$ (c 0.23, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.10 (br s, 1H), 2.47 (ddd, 1H, $J = 3.5$, 5.3, 13.2 Hz), 2.70 (dt, 1H, $J = 9.1$, 13.2 Hz), 3.12 (ddt, 1H, $J = 4.1$, 5.3, 8.8 Hz), 3.58 (m, 2H), 3.95 (d, 1H, $J = 14.1$ Hz), 4.05 (d, 1H, $J = 14.1$ Hz), 4.73 (dd, 1H, $J = 3.5$, 9.1 Hz), 7.29–7.32 (m, 5H); δ_C (100 MHz, $CDCl_3$): 36.8, 60.6, 61.6, 64.2, 65.5, 118.6, 128.6, 128.7, 127.6, 135.8. Anal. Calcd for $C_{12}H_{14}N_2O_2$ (218.25): C, 66.04; H, 6.47; N, 12.84. Found: C, 66.19; H, 6.33; N, 12.61.

4.14. (3*R*,5*S*)-2-Benzyl-3-(*tert*-butoxydiphenylsiloxymethyl)-5-cyanoisoxazolidine 20

To a solution of **19** (50 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) were added *tert*-butyldiphenylsilyl chloride (70 mg, 0.25 mmol), Et_3N (30 mg, 0.3 mmol), and DMAP (8 mg, 0.07 mmol). The resulting solution was stirred at ambient temperature for 12 h at which time 0.1 M HCl (10 mL) was added. The organic layer was separated and washed with brine (10 mL), dried over $MgSO_4$, and evaporated to afford the crude product. Purification by radial chromatography (hexane/EtOAc, 90:10) furnished pure **20** (84 mg, 80%) as an oil. $[\alpha]_D = +60$ (c 0.19, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.06 (s, 9H), 2.38 (ddd, 1H, $J = 3.5$, 6.5, 13.0 Hz), 2.70 (dd, 1H, $J = 9.4$, 13.0 Hz), 3.13 (dddd, 1H, 4.9, 5.6, 6.5, 6.6 Hz, H_3), 3.75 (dd, 1H, $J = 4.9$, 10.7 Hz), 3.83 (dd, 1H, $J = 6.6$, 10.7 Hz), 3.90 (d, 1H, $J = 14.6$ Hz), 4.35 (d, 1H, $J = 14.6$ Hz), 4.73 (dd, 1H, $J = 3.5$, 8.8 Hz), 7.29–7.42 (m, 11H), 7.60–7.66 (m, 4H); δ_C (100 MHz, $CDCl_3$): 19.2, 26.9, 37.8, 61.0, 63.6, 64.6, 65.4, 118.9, 127.3, 127.8, 127.9, 128.3, 128.4, 129.9 (2C), 132.8 (2C), 135.5, 135.6, 136.7. Anal. Calcd for $C_{28}H_{32}N_2O_2Si$ (456.65): C, 73.64; H, 7.06; N, 6.13. Found: C, 73.55; H, 7.21; N, 6.02.

4.15. (3*R*,5*S*)-3-(*tert*-Butoxydiphenylsiloxymethyl)-5-cyanoisoxazolidine 21

To a solution of **18d** (0.45 g, 0.6 mmol) in MeOH (15 mL), *p*-toluenesulfonic acid (0.17 g, 0.9 mmol) was added and the solution refluxed for 2 h. Then, after cooling, the solution was evaporated to dryness. The obtained crude product was pure enough to be used in the next step without further purification. δ_H (300 MHz, $CDCl_3$): 1.02 (s, 9H), 2.52 (m, 2H, H_4), 3.35 (m, 1H, H_3), 3.82 (dd, 1H, $J = 3.5$, 11.3 Hz), 3.96 (dd, 1H, $J = 3.1$, 11.3 Hz), 4.90 (t, 1H, $J = 6.8$ Hz, H_5), 6.01 (br s, 1H, NH), 7.20–7.60 (m, 10H); δ_C (75 MHz, $CDCl_3$): 19.3, 25.6, 37.9, 62.3, 65.4, 75.0, 119.2, 128.4, 130.3, 134.8.

4.16. *N*-Benzylation of 21

To a solution of **21**, obtained from **18d** (0.45 g, 0.6 mmol), in CH_2Cl_2 (20 mL), triethylamine (0.082 mL, 0.6 mmol), and benzyl bromide (0.071 mL, 0.6 mmol) were added and the solution stirred for 2 h at room temperature. The solution was extracted with CH_2Cl_2 (2×20 mL). The organic phase was separated, washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by column chromatography (hexane/EtOAc, 9:1) to afford 260 mg (96%, two steps) of pure **20** as an oil. The physical and spectroscopic properties were identical to those observed for the same compound prepared from **19** as described above.

4.17. (3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(*tert*-butyldiphenylsiloxymethyl)-5-[(4*RS*)-4-(ethoxycarbonyl)-2-thiazolin-2-yl]isoxazolidine 22 (mixture of epimers)

Treatment of **18d** (0.5 g, 0.64 mmol) under the conditions described above for the preparation of **9a** gave after chromatography (hexane/EtOAc, 80:20) 0.407 g (70%) of **22** as an oil which was, after ^1H NMR identification, promptly used for the further step. δ_H (300 MHz, $CDCl_3$): 1.02 (s, 18H), 1.26 (s, 3H), 1.30 (t, 3H, $J = 6.2$ Hz), 1.32 (s, 3H), 2.01 (m, 2H), 2.95 (dd, 1H, $J = 7.4$, 13.4 Hz), 3.11 (dd, 1H, $J = 4.5$, 13.4 Hz), 3.20–3.40 (m, 3H), 3.81 (dd, 1H, $J = 4.5$, 7.4 Hz), 4.13 (m, 1H), 4.15 (q, 2H, $J = 6.2$ Hz), 4.80–4.90 (m, 3H), 4.92 (m, 1H), 5.01 (m, 1H), 7.22–7.36 (m, 12H), 7.53–7.60 (m, 8H).

4.18. (3*R*,5*S*)-2-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(*tert*-butyldiphenylsiloxymethyl)-5-[(4*S*)-4-(ethoxycarbonyl)-2-thiazolyl]isoxazolidine 23

Treatment of **22** (0.4 g, 0.44 mmol) under the conditions described above for the preparation of **10a** gave after chromatography (hexane/EtOAc, 80:20) 0.36 g (90%) of pure **23** as an oil. $[\alpha]_D = -19$ (c 0.24, $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 1.02 (s, 18H), 1.26 (s, 3H), 1.40 (t, 3H, $J = 7.2$ Hz), 1.41 (s, 3H), 2.22 (ddd, 1H, $J = 4.1$, 6.0, 12.9 Hz), 2.85 (ddd, 1H, $J = 4.5$, 6.0, 12.9 Hz), 3.30–3.40 (m, 5H), 4.02 (m, 1H), 4.35 (q, 2H, $J = 7.2$ Hz), 4.60 (m, 2H), 4.78 (d, 1H, $J = 0.6$ Hz), 5.5 (dd, 1H, $J = 4.5$, 6.02 Hz), 7.20–7.35 (m, 12H), 7.43–7.62 (m, 8H), 7.95 (s, 1H) ; δ_C (75 MHz, $CDCl_3$): 14.1, 19.2, 25.6, 26.5, 39.3, 60.2, 62.7, 62.9, 63.00, 81.2, 83.3, 83.4, 86.2, 111.2, 124.2, 127.7, 129.8, 129.9, 133.0, 134.8, 135.4, 135.5, 168.0, 170.2. Anal. Calcd for $C_{50}H_{62}N_2O_8SSi_2$ (907.27): C, 66.19; H, 6.89; N, 3.09. Found: C, 65.96; H, 6.91; N, 3.23.

4.19. (3*R*,5*S*)-3-(Hydroxymethyl)-5-[4-(aminocarbonyl)-2-thiazolyl]isoxazolidine *ent*-5

Ammonia gas was bubbled through a well stirred solution of **23** (0.3 g, 0.33 mmol) in MeOH (15 mL) at room temperature. After 1 h, the reaction mixture was evaporated under reduced pressure to dryness. The residue was dissolved in a 1.5% HCl solution in EtOH (10 mL), and the reaction mixture stirred at room temperature for 3 h. The solution was brought to pH 10 by adding aq 10% sodium carbonate and extracted with CH_2Cl_2 (2×10 mL). The organic phase was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by column chromatography ($CHCl_3$/MeOH, 10:1) to afford 50 mg (95%) of pure *ent*-**5** as an oil. $[\alpha]_D = +20$

(c 0.17, MeOH); δ_H (300 MHz, 1:1 $CDCl_3$–CD_3OD) 1.98 (ddd, 1H, $J = 5.0$, 5.4, 11.9 Hz), 2.05 (ddd, 1H, $J = 5.9$, 6.0, 11.9 Hz), 2.72 (dddd, 1H, $J = 4.5$, 4.9, 5.4, 5.9 Hz), 3.60 (dd, 1H, $J = 4.5$, 9.8 Hz), 3.82 (dd, 1H, $J = 4.9$, 9.8 Hz), 4.5 (dd, 1H, $J = 5.0$, 6.0 Hz), 7.89 (s, 1H); δ_C (75 MHz, 1:1 $CDCl_3$–CD_3OD) 41.2, 62.1, 64.4, 87.9, 124.0, 149.4, 160.2 170.2. Anal. Calcd for $C_8H_{11}N_3O_3S$ (229.26): C, 41.91; H, 4.84; N, 18.33. Found: C, 41.78; H, 5.01; N, 18.56.

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27. Interestingly, the (5*S*)-configuration of the major adducts is opposite to that found by Vasella (see Ref. 16) for the cycloaddition between *N*-ribosyl-*C*-(alkoxymethyl) nitrones and methyl methacrylate, thus pointing out the influence in the diastereofacial selectivity of the reaction not only of the chiral auxiliary but also of the dipolarophile's nature.
28. Attempts of deprotecting the *N*-benzyl group included hydrogenation under mild conditions and reduction with Na and Li in liquid ammonia. A less common method, such as Montmorillonite K-10, which had successfully been used by us with other *N*-benzyl isoxazolidinyl nucleosides (see Ref. 8c) was also tested. In all cases complex reaction mixtures were obtained.
29. Furthermore, the use of different *N*-glycosyl units, such as mannosyl, gulosyl, or erythrosyl derivatives, which are available in both enantiomeric forms, could provide access to both enantiomeric series. For representative examples of the use of those nitrones, see: (a) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 2225–2233; (b) Cicchi, S.; Marradi, M.; Corsi, M.; Faggi, C.; Goti, A. *Eur. J. Chem.* **2003**, 4152–4160, see also Ref. 16.
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