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# Zinc(II) Triflate-Controlled 1,3-Dipolar Cycloadditions of *C*-(2-Thiazolyl)nitrones: Application to the Synthesis of a Novel Isoxazolidinyl Analogue of Tiazofurin

Ugo Chiacchio,*,† Antonio Rescifina,† Maria G. Saita,† Daniela Iannazzo,‡ Giovanni Romeo,*,‡ Juan A. Mates,§ Tomas Tejero,§ and Pedro Merino*,§

*Dipartimento di Scienze Chimiche, Università di Catania, Viale Andrea Doria 6, 95125 Catania, Italy, Dipartimento Farmaco-Chimico, Università di Messina, Viale SS. Annunziata, 98168 Messina, Italy, and Departamento de Quimica Organica, Facultad de Ciencias, ICMA, Universidad de Zaragoza, CSIC, E-50009 Zaragoza, Aragon, Spain*

*pmerino@unizar.es*

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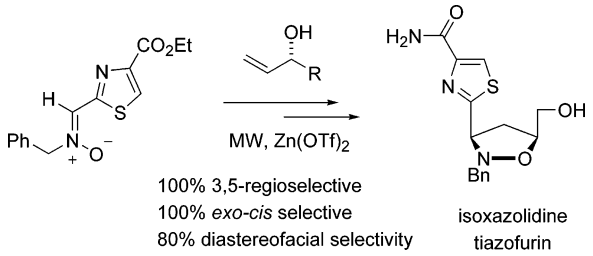


The cycloaddition reaction between *C*-(2-thiazolyl) nitrones and allylic alcohol takes place with complete exo selectivity when the reactions are carried out in the presence of 1 equiv of zinc triflate. The rate of the reaction is increased enormously under microwave irradiation. The use of a chiral dipolarophile allowed application of the methodology to the synthesis of a hitherto unknown enantiomerically pure isoxazolidinyl analogue of the *C*-nucleoside tiazofurin.

## Introduction

Numerous naturally occurring and synthetic *C*-nucleosides display potent antitumoral and/or antiviral activities.[1] Among them, tiazofurin **1** has demonstrated potent antitumor activity against several human cancers including myeloid leukemia.[2] From the first synthesis of **1** reported by Robins and co-workers in 1977,[3] several synthetic approaches have been reported for that compound.[2] To improve its biological properties, several analogues of **1** have also been prepared. Thus, modifications in the substitution on the carbohydrate moiety[4] and changes of the C-linked heterocycle, acting as a base,[5] have been reported. In another class of nucleosides, the natural ribose unit has been replaced with a different heterocyclic moiety. In particular, Kini and co-workers[6] reported the synthesis of aza tiazofurin **2**, and Chu and co-workers[7] prepared the corresponding 1,3-dioxolanyl derivative **3** (Chart 1).

* To whom correspondence should be addressed. Tel.: +34 976 762075. Fax: +34 976 762075.
† Università di Catania.
‡ Università di Messina.
§ Universidad de Zaragoza.

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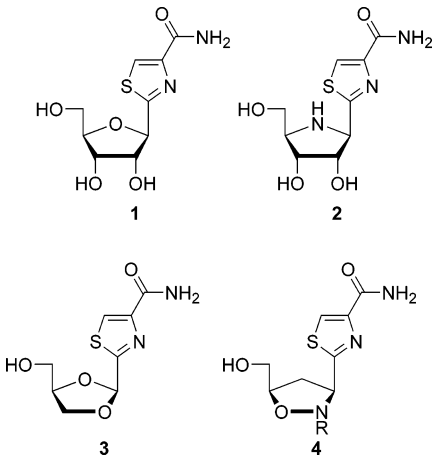
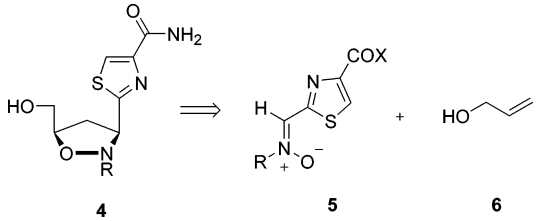
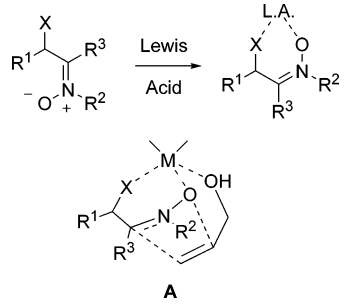
**CHART 1. Tiazofurin and Its Analogues**



**SCHEME 1. Retrosynthetic Analysis of Isoxazolidinyl Tiazofurin**



**SCHEME 2. Lewis Acid-Mediated Cycloaddition**



The heterocyclic nucleosides[8] have gained considerable attention during the last years,[9] and, among them, the isoxazolidinyl analogues and related compounds show great promise as drug candidates.[10] For some years, our groups have been investigating on the development of efficient and flexible synthesis of isoxazolidinyl nucleosides[11] including psiconucleosides,[12] amino acid nucleosides,[13] and *C*-nucleosides.[14] Within the last context, we have recently published the synthesis of isoxazolidinyl pseudouridines.[15]

Following our interest in isoxazolidinyl nucleosides, we report in this Article the synthesis of **4** (R = Bn), the first member of a new series of tiazofurin analogues containing an isoxazolidine ring as a spacer between the thiazole-4-carboxamide unit and the hydroxymethyl group.

According to our preliminary studies on the synthesis of isoxazolidinyl-*C*-nucleosides[14] and the retrosynthetic analysis depicted in Scheme 1, we needed for the construction of **4** the corresponding *N*-benzyl-*C*-(4-ethoxycarbonyl-2-thiazolyl) nitrone **5**. Cycloaddition of this nitrone with allylic alcohol under the appropriate conditions should lead to an immediate precursor of the target compound.

It has been well documented by previous work from our[14] and other[16] laboratories that Lewis acids could be used to control the endo/exo selectivity in cycloadditions between allylic alcohol and nitrones bearing a coordinating group at the nitrone carbon atom (Scheme 2).

These nitrones include *C*-(ethoxycarbonyl) and *C*-heteroaryl nitrones such as 2-pyridyl and 2-quinolyl. A general transition state **A** as illustrated in Scheme 2 could explain the observed selectivities in favor of the exo adducts. Also, the hydroxyl group of the allylic alcohol is suitable of participating in complexation with the catalyst.[14]

In view of the above, we embarked on the search of the best conditions for making *cis*-selective the cycloaddition between allylic alcohol and *C*-(2-thiazolyl) nitrone **5**. We also describe synthetic approaches for the preparation of enantiomerically pure **4** by introducing chiral groups/auxiliaries at either the nitrone moiety or the dipolarophile. Some mechanistic consideration based on semiempirical calculations is reported, too.

## Results and Discussion

Nitrone **5** is easily obtained by condensation of the corresponding aldehyde and *N*-benzylhydroxylamine. The known[17] aldehyde **10** was prepared by a classical

(8) The term heterocyclic nucleosides refers to nucleoside analogues in which the furanose ring has been replaced by a different heterocyclic ring. For a review on this topic, see ref 9a.

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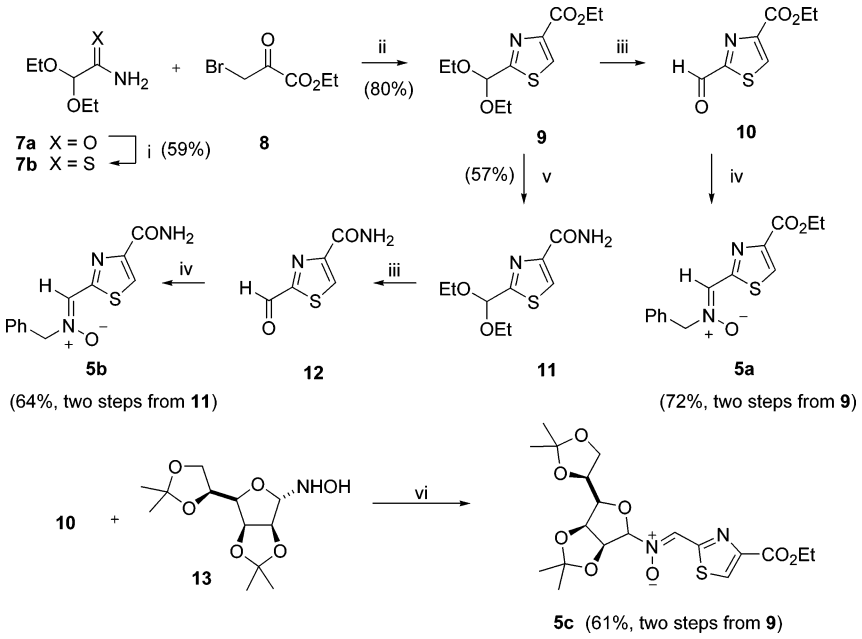
**SCHEME 3. Synthesis of *C*-(2-Thiazolyl) Nitrones**[a]




[a] Reagent and conditions: (i) $P_2S_5$, $C_6H_6$. (ii) EtOH, MS 4 Å. (iii) 1 M HCl, acetone, reflux. (iv) $PhCH_2NHOH$, $CH_2Cl_2$, $MgSO_4$. (v) $NH_3$, MeOH. (vi) $PhCH_2NHOH$, $CH_2Cl_2$, $MgSO_4$, reflux.

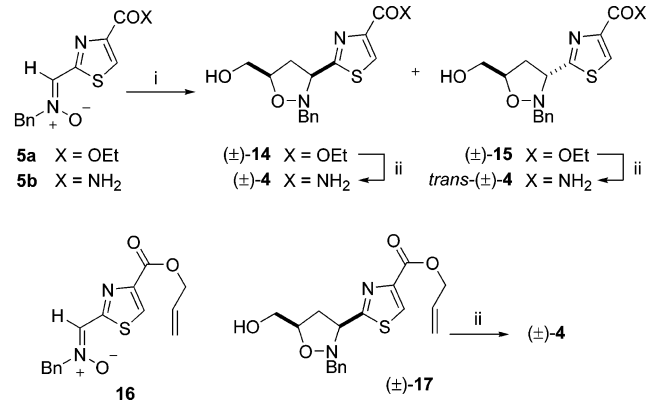
Hantszch's synthesis from diethoxyacetamide **7a** and ethyl 3-bromopyruvate **8**, and further acidic treatment (Scheme 3).

Condensation of **10** with *N*-benzylhydroxylamine[18] afforded the hitherto unknown nitrone **5a** in 90% yield. Because the final nucleoside analogue should bear a carboxamide group at the thiazole ring, we also considered the possibility of introducing such a group at an earlier stage. Thus, intermediate **9** was transformed into **11** by the action of methanolic ammonia. Acidic hydrolysis of **11** gave aldehyde **12**, which afforded nitrone **5b** after condensation with *N*-benzylhydroxylamine. To introduce a chiral auxiliary at the nitrone moiety, D-mannofuranosyl hydroxylamine **13**[19] was also condensed with **10** leading to chiral nonracemic nitrone **5c**. The configuration of nitrones **5** was unambiguously established by NOE experiments. The irradiation of the azomethine proton led to 8−12% enhancements of the signal corresponding to the benzyl (in **5a** and **5b**) or anomeric (in **5c**) protons, thus indicating a *Z*-configuration in all cases.

The 1,3-dipolar cycloaddition reaction of nitrones **5a** and **5b** with allylic alcohol (Scheme 4) was screened to optimize the reaction. The results are collected in Table 1.

Condensation of **5a** with 10 equiv of allylic alcohol in a sealed tube at 60 °C using dichloromethane as a solvent (entry 1) afforded after 25 days a 63:37 mixture of cis/trans adducts **14** and **15**. In the absence of solvent and at 160 °C (entry 2), a similar ratio was obtained in a considerable lower, but still long, reaction time (15 days). An identical result was obtained with nitrone **5b** (entry 7). It is well-known that microwave irradiation in cycloaddition reactions considerably reduces reaction times

**SCHEME 4. Cycloaddition Reaction of Nitrones 5a,b with Allylic Alcohol**[a]




[a] Reagent and conditions: (i) allylic alcohol (see Table 1). (ii) $NH_3$, MeOH.

and may affect product ratios and yields.[20] Application of this technique to the reaction shown in Scheme 4 resulted in a considerable acceleration of the process. When the reaction was performed under solvent-free conditions at 160 °C, the cycloaddition of nitrones **5a** and **5b** went to completion in 1 and 3 h, respectively (entries 3 and 8). However, also in this case a low cis/trans ratio (60:40) was observed. The addition of $MgBr_2 \cdot Et_2O$ (entry 4), following the Kanemasa's conditions,[21] only afforded, after 3 days, the nitrone **16** in which the ethyl ester moiety had been transesterified with allylic alcohol. Additional time of reaction did not lead to any cyclo-

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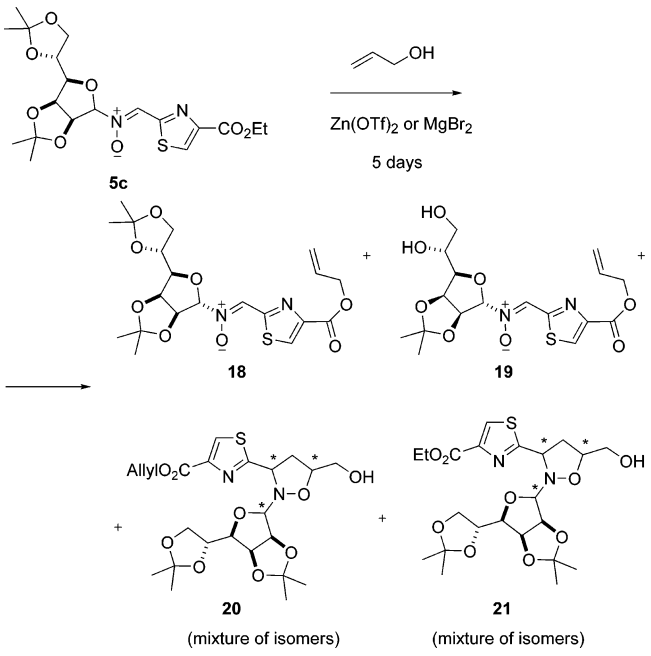
**TABLE 1. Cycloaddition between Nitrones 5a and 5b and Allylic Alcohol[a]**

| entry | nitrone | solvent | Lewis acid[b] | temp (°C) | MW (watts)[c] | time | **14**:**15** | yield (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **5a** | $CH_2Cl_2$ | none | 60 | | 25 d | 63:37 | 70 |
| 2 | **5a** | neat | none | 160 | | 15 d | 60:40 | 68 |
| 3 | **5a** | neat | none | 120 | 90 | 1 h | 60:40 | 80 |
| 4 | **5a** | $CH_2Cl_2$ | $MgBr_2$ | 80 | | 3 d | | |
| 5 | **5a** | $CH_2Cl_2$ | $Zn(OTf)_2$ | 80 | | 4 d | 100:0 | 90[e] |
| 6 | **5a** | $CH_2Cl_2$ | $Zn(OTf)_2$ | 120 | 90 | 15 min | 100:0 | 90[e] |
| 7 | **5b** | neat | none | 160 | | 20 d | 63:37 | 40 |
| 8 | **5b** | neat | none | 120 | 90 | 3 h | 60:40 | 60 |
| 9 | **5b** | $CH_2Cl_2$ | $Zn(OTf)_2$ | 160 | 90 | 15 min | 100:0 | 55 |

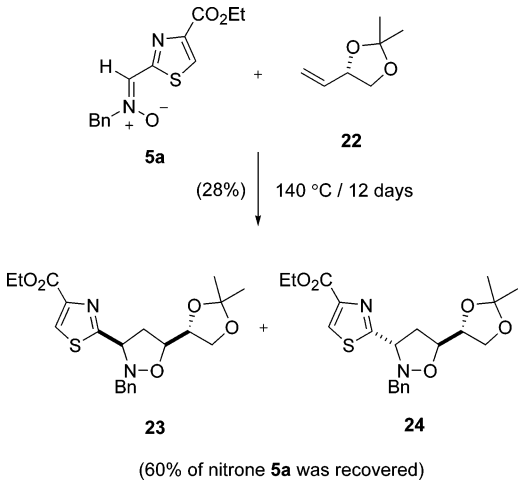
[a] All reactions were carried out in a sealed tube. [b] 1.0 equiv was used. [c] The reactions were carried out in a microwave reactor. [d] Isolated yield. [e] Compounds **14** and **17** were obtained in 54% and 36% yields, respectively (corresponding to a 90% yield for the cycloaddition reaction).

**SCHEME 5. Cycloaddition Reaction of Nitrone 5c with Allylic Alcohol**




addition product. On the other hand, when the reaction was conducted in the presence of 1.0 equiv of $Zn(OTf)_2$ (entry 5), it went to completion in 4 days. A complete cis selectivity was obtained, although the two adducts **14** and **17** were obtained in 54% and 36% isolated yields, respectively. Even though the two adducts can be easily separated by chromatographic methods, for synthetic purposes it is preferable to treat the mixture with methanolic ammonia to yield compound (±)-**4** in quantitative yield. Next, we considered taking advantage of the two accelerating factors; thus, we carried out the reaction both in the presence of $Zn(OTf)_2$ and under microwave irradiation (entries 6 and 9) using dichloromethane as a solvent. Under these conditions, a substantial improvement was finally achieved and the reaction finished after only 15 min. Whereas the nitrone **5a** afforded the same mixture of cis adduct **14** and transesterified product **17** that have been obtained without microwave irradiation, the nitrone **5b** afforded only (±)-**4** in 55% chemical yield. This lower chemical yield can be explained by the lower solubility of nitrone **5b**. From a synthetic point of view, it is more advisable to carry out the reaction with nitrone **5a** and treat the obtained mixture with methanolic ammonia to obtain the target

**SCHEME 6. Cycloaddition Reaction of Nitrone 5a with Homochiral Alkene 22**

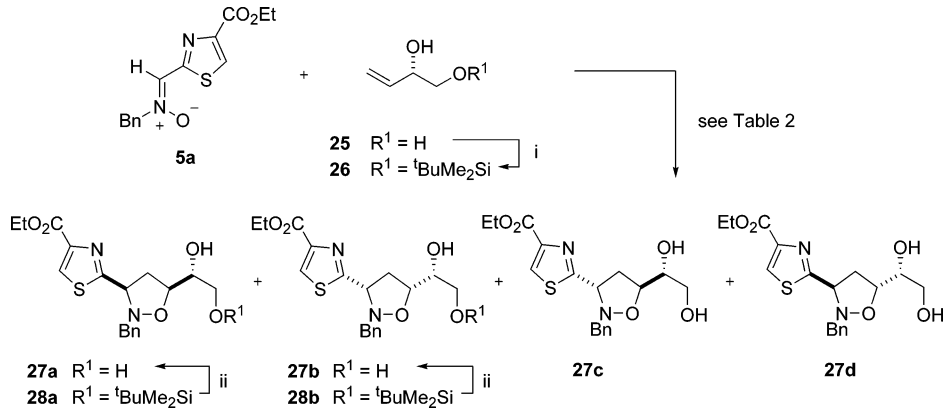



compound in 90% overall yield (two steps). The relative stereochemistry of compounds (±)-**4**, **14**, and **15** were deduced from detailed NMR studies including HMQC $^{13}C-^{1}H$, COSY, and NOE.

The final goal of this work was to develop a synthetic route to unknown enantiomerically pure isoxazolidinyl tiazofurin. For this, we applied this synthetic protocol to enantiopure substrates. First, we checked the cycloaddition of **5c** with allylic alcohol in the presence of 1.0 equiv of $Zn(OTf)_2$ (Scheme 5). After 5 days of reaction, no more starting nitrone was observed (TLC) and the reaction was stopped. After a usual workup, a quite complex crude mixture was obtained.

Assessment of cycloaddition diastereoselectivity was difficult due to the complexities in the $^{1}H$ NMR spectra of N-sugar compounds. This was in part due to dynamic properties associated with nitrogen inversion (in the isoxazolidine) that was shown on the NMR time scale. Semipreparative HPLC allowed the separation of four peaks consisting of transesterified nitrones **18** and **19** and two mixtures **20** and **21** that could not be separated. New methylene signals for these mixtures appeared in the range 2.0−3.6 ppm, which were only possible for 3,5-disubstituted isoxazolidines. At a $^{1}H$ NMR probe temperature of 55 °C, the resonances in the isolated mixtures **20** and **21** were considerably sharpened and had baseline separation, which allowed quantification of the diastereomers. The presence of up to five different compounds in each mixture indicated not only poor cis/trans and diastereofacial selectivities but also epimerization at the

**SCHEME 7. Cycloaddition Reaction of Nitrone 5a with Homochiral Alkenes 25 and 26**[a]




[a] Reagents and conditions: (i) $^t$BuMe$_2$SiCl, imidazole, DMF. (ii) Bu$_4$NF, THF.

**TABLE 2. Cycloaddition between Nitrone 5a and Alkenes 25 and 26**[a]

| entry | alkene | solvent | Lewis acid[b] | time (h) | **a**:**b**:**c**:**d** | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **25** | $CH_2Cl_2$ | none | 3 | | *d* |
| 2 | **25** | $CH_2Cl_2$:EtOH | none | 1 | 1:1:2:2 | 60 |
| 3 | **25** | $CH_2Cl_2$ | $Zn(OTf)_2$ | 1 | | *d* |
| 4 | **26** | $CH_2Cl_2$ | $Zn(OTf)_2$ | 2 | 4:1:0:0 | 70 |

[a] All reactions were carried out in a sealed tube at 120 °C under microwave irradiation (90 W). [b] 1.0 equiv was used. [c] Isolated yield. [d] No reaction was observed.

anomeric center of the sugar moiety. Due to these disappointing results, the N-sugar approach was definitively discarded.

We therefore sought to explore the reactivity of nitrone **5a** with chiral dipolarophiles. 1,3-Dipolar cycloaddition of **5a** with alkene **22** gave adducts **23** and **24** (Scheme 6).

The absolute configuration of compounds **23** and **24** was subsequently confirmed upon deacetalyzation and comparison of the resulting diols with further assigned identical compounds (see below). The reaction was extremely low, because after 12 days at 140 °C (sealed tube) only 28% of conversion was observed. The diastereomeric cis/trans ratio was only near 2:1 but the diastereofacial induction was excellent; only anti adducts (with respect to the stereogenic center of the dipolarophile) were observed.

Unfortunately, the cis/trans selectivity of the reaction was not affected by the presence of Lewis acids, identical results being obtained when the reaction was carried out in the presence of 1.0 equiv of $Zn(OTf)_2$ or $MgBr_2{\cdot}Et_2O$. These results further confirm the necessity of a hydroxyl group at an allylic position to control the endo/exo selectivity of the reaction.

We next examined cycloaddition of **5a** with commercially available (2*S*)-1,2-dihydroxy-3-butene **25** (Scheme 7, Table 2). No reaction was observed under microwave irradiation when dichloromethane was used as a solvent either in the presence of or in the absence of $Zn(OTf)_2$ (entries 1 and 3). On the other hand, when a 1:1 $CH_2Cl_2$:EtOH mixture was used as a solvent (entry 2), the reaction went to completion in 30 min and a 1:1:2:2 mixture of the four possible diastereomers **27** was obtained. These compounds were easily separated by chromatographic methods and fully characterized. Addition of $Zn(OTf)_2$ to this reaction resulted in only decomposition products, quite probably because of a chelation between the diol and the Lewis acid as well as the incompatibility of using $Zn(OTf)_2$ in the presence of ethanol.

To find conditions similar to those previously found for allylic alcohol, the silylated compound **26**[22] was ultimately considered to be the optimum compound. This was prepared from diol **25** by selective silylation of the primary hydroxyl group. Cycloaddition between nitrone **5a** and **26** under microwave irradiation and in the presence of $Zn(OTf)_2$ afforded a 4:1 mixture of cis adducts **28a** and **28b**. Again, a complete cis selectivity was observed in the reaction as evidenced by proton NMR and NOE studies. The observed diastereofacial selectivity (80% in favor of the (3*R*,5*S*)-isomer **28a**) rendered the process synthetically useful.

The absolute configuration of compounds **27** has been assigned by NMR techniques and by circular dichroism. We reported[23] a sector rule for the circular dichroism of the thiazole chromophore in a variety of 2-thiazolylcarbinamines. According to that sector rule, which matches those proposed by us[24] for similar furan derivatives and by Smith and co-workers[25] for phenylcarbinamines, the observed Cotton effect in the range 210−230 nm for adducts **27a** and **27d** is consistent with the (*R*)-configuration at C-3 of the isoxazolidine ring (Figure 1).

The observed negative Cotton effect in the same range for compounds **27b** and **27c** is consistent with the (*S*)-configuration. These data were also in good agreement with those reported by Holzapfel and co-workers for compounds with a 4-carboxythiazole as a chromophore.[26]

The relative cis/trans configuration of the isoxazolidine rings was determined by NOE experiments. The stereochemical assignments for compounds **28a** and **28b** were

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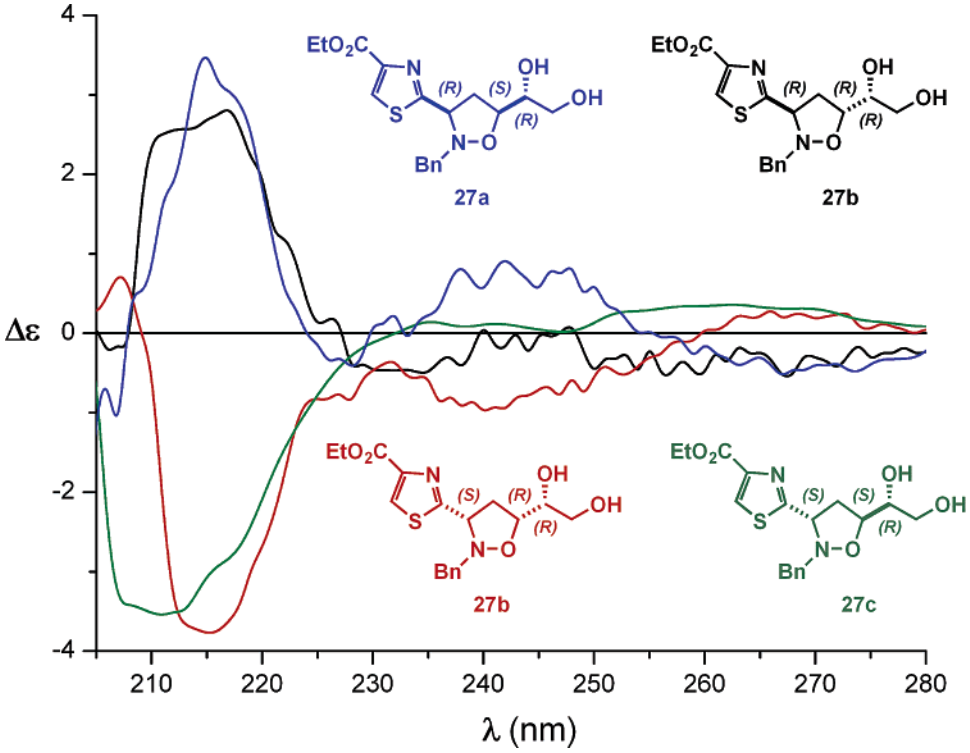
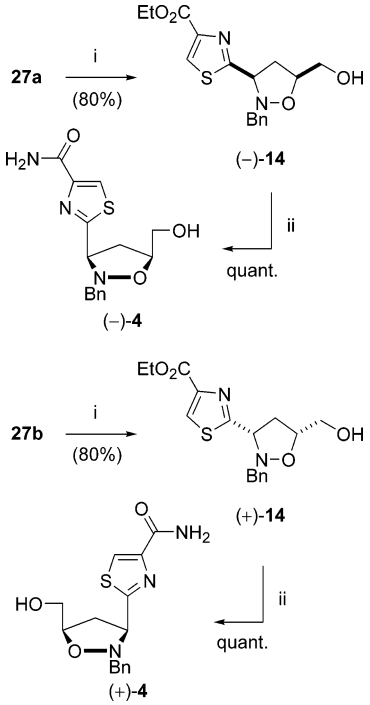



**FIGURE 1.** CD spectra of compounds **27**.

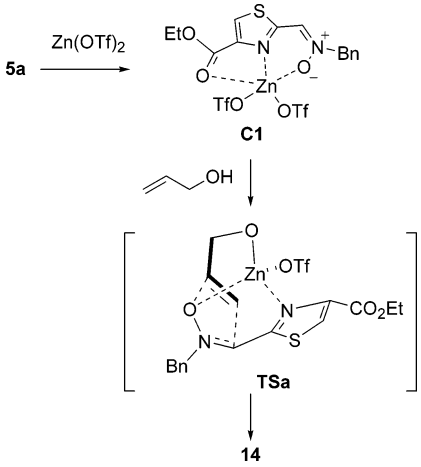
**SCHEME 8. Synthesis of Both Enantiomers of Isoxazolidinyl Analogue of Tiazofurin**[a]




[a] Reagents and conditions: (i) $NaIO_4$, MeOH−$H_2O$ then $NaBH_4$, MeOH. (ii) $NH_3$, MeOH.

made by comparison of the corresponding desilylated products with **27a** and **27b**, respectively. With the (3*R*,5*S*)-isoxazolidine **27a** efficiently in hand, its transformation to the targeted enantiomerically pure isoxazolidinyl analogue **4** only remained. This was achieved by

**SCHEME 9. Proposed TS for the Reaction between 5a and Allylic Alcohol**




treatment of **27a** with sodium periodate and in situ reduction of the formed aldehyde.

The resulting alcohol (−)-**14** was transformed into isoxazolidinyl analogue of tiazofurin (−)-**4** in quantitative yield (Scheme 8). To further confirm the stereochemical assignment, compound **27b** was also obtained from desilylation of the minor adduct **28b** and transformed into (+)-**14** and then (+)-**4** following the same reaction sequence.

The above overall results suggested a confirmation of our previous studies carried out with *C*-(2-pyridyl) nitrones.[14] A free hydroxyl group is needed to achieve a complete exo selectivity according to previously proposed mechanisms through a transition state as outlined in Scheme 2. A complete mechanism of the cycloaddition between nitrone **5a** and allylic alcohol promoted by

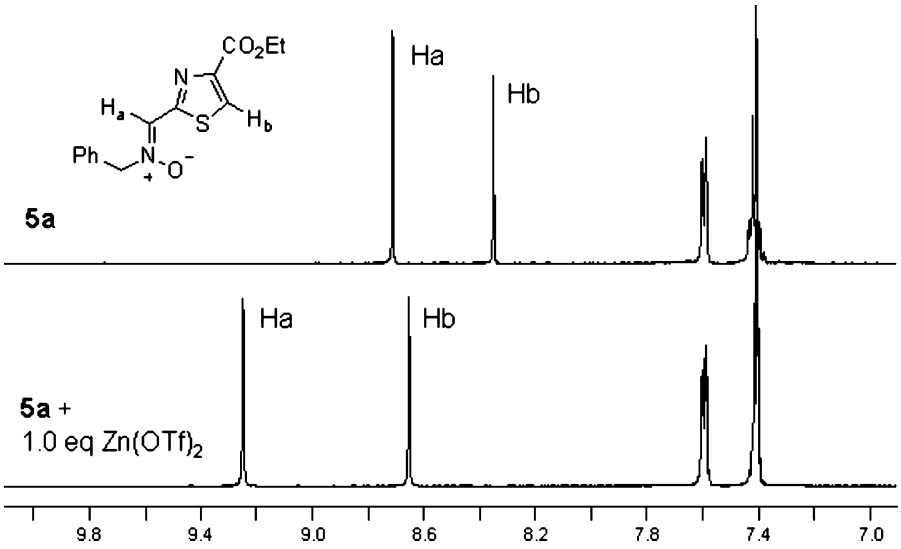


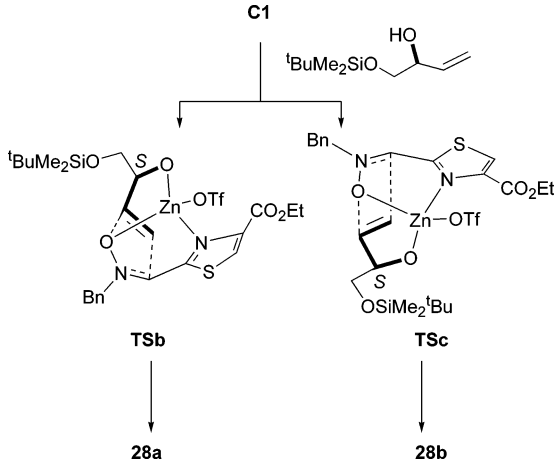

**FIGURE 2.** NMR spectra of nitrone **5a** before (up) and after (down) the addition of 1 equiv of zinc(II) triflate (NMR spectra recorded in acetone-$d_6$ at 25 °C).

$Zn(OTf)_2$ is proposed in Scheme 9. In the case of nitrone **5a**, a complex **C1** was formed, in which the nitrone oxygen is bound to the zinc atom forming a chelate with the nitrogen thiazole atom.

Experimental evidence of this complex was provided by comparison of NMR spectra of nitrone **5a** in the absence and in the presence of 1.0 equiv of zinc(II) triflate (Figure 2).[27] Thus, the formation of **C1** was substantiated by the observation of the signal due to the azomethine proton, which is shifted downfield ($\Delta\delta$ = 0.54 ppm) as compared to that of the nonchelated nitrone and by the same effect ($\Delta\delta$ = 0.30 ppm) observed for the proton of the thiazole ring. The observed downfield shifts are in agreement with reported identical effects in other *C*-hetaryl nitrones.[28] In addition, from the $^{13}C$ NMR spectra of the free nitrone and complex **C1**, it can be seen that the resonance of the C=O carbon of the ester moiety is shifted downfield by ca. 5 ppm. This also provides evidence that the ester moiety is also bound to the zinc atom in solution. Such a coordination of the ester unit to the metal atom can justify the observed transesterification with allylic alcohol, which presumably occurs, in some extent, after the cycloaddition process. According to our previous findings[14] with *N*-benzyl-*C*-(2-pyridyl) nitrone, it is possible to propose an intramolecular exo transition structure **TSa** leading to the cis adduct as the only product of the reaction (Scheme 9).

The $\pi$-facial selectivity of the cycloaddition reactions with homochiral **26** is controlled by the protected hydroxymethyl moiety. In this case, the transesterification reaction could be disfavored due to steric interactions of the siloxymethyl group, and this could be the reason no transesterified products are found in the cycloaddition with **26**. Starting from complex **C1**, two possible transition states **TSb** and **TSc** are possible leading to the cis isomers **28a** and **28b**, respectively (Scheme 10).

**SCHEME 10. Proposed TSs for the Reaction between 5a and Alkene 26**




We also checked the validity of these hypothesis by performing semiempirical calculations (PM3) of the whole process.[29] These calculations (PM3) point out the *Si* face of the alkene as the less hindered one in a good agreement with the observed experimental results.

## Conclusions

In summary, the present study provides an insight into the way in which *C*-(2-thiazolyl) nitrones undergo Lewis acid-controlled cycloadditions with allylic alcohols. A considerable acceleration of the process is achieved by the use of both the Lewis acid and microwaves. The reaction has been shown to be highly regio- and stereoselec-

(27) The sample was prepared by dissolving the nitrone in acetone-$d_6$ and adding 1.0 equiv of $Zn(OTf)_2$ at ambient temperature under an argon atmosphere. The resulting solution was stirred manually, and the NMR was recorded at the same temperature immediately.

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(29) Semiempirical methods are intended for studying large and complicated molecular systems of interest for which a complete application of the ab initio methods is generally prohibitive in terms of computational effort. Several studies have suggested semiempirical methods as a good choice for studying cycloaddition processes and to make general and qualitative estimation of the course of the reaction. The complete calculations can be obtained from the authors.

tive, providing a synthetically useful entry into racemic and homochiral new nucleoside analogues of tiazofurin.

## Experimental Section

**General.** 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 was 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 solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel, TLC grade, with binder and fluorescence indicator, and the eluting solvents were delivered by the pump at a flow-rate of 0.5−1.5 mL $min^{-1}$. Column chromatography was carried out in a MPLC system using silica gel 5−60 $\mu$m. Melting points were uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz instrument in $CDCl_3$. Chemical shifts are reported in ppm ($\delta$) relative to $CHCl_3$ ($\delta = 7.26$) in $CDCl_3$. Optical rotations were taken at 25 °C.

**Diethoxythioacetamide 7b.** To a solution of diethoxyacetamide **7a** (16 g, 0.108 mmol) in dry benzene (200 mL) was added $P_2S_5$ (8 g, 36 mmol) portionwise with stirring during a period of 10 min. After the mixture was stirred at ambient temperature for an additional 10 min (color changed from yellow to violet), an insoluble material was removed by decantation. The solution was washed with saturated aq $NaHCO_3$ (2 × 605 mL) and brine (2 × 60 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. A red solid was remaining. The residue was recrystallized from benzene/hexane (1:1) to give 10.4 g (59%) of pure **7** as red needles. Mp 54−56 °C. $\delta_H$ (400 MHz, $CDCl_3$) 1.25 (t, 6H, $J$ = 7.0 Hz), 3.65 (q, 4H, $J$ = 7.0 Hz), 5.05 (s, 1H), 7.55 (s, 1H), 7.85 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.9, 62.9, 103.1, 201.9. Anal. Calcd for $C_6H_{13}NO_2S$: C, 44.15; H, 8.03. Found: C, 44.52; H, 7.88.

**Ethyl-2-(diethoxymethyl)thiazole-4-carboxylate 9.** A solution of **7** (7.8 g, 23.5 mmol) in absolute ethanol (200 mL) was treated with ethyl-3-bromopyruvate **8** (8.85 g, 48.9 mmol) and activated 4 Å molecular sieves (8.0 g). The resulting mixture was refluxed for 90 min and then filtered and concentrated in a vacuum. The residue was partitioned between EtOAc (100 mL) and saturated aq $NaHCO_3$ (50 mL). The organic layer was separated and washed with brine (2 × 50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (gradient hexane/EtOAc 80:20 to 100% EtOAc) to give pure **9** (4.87 g, 80%) as a yellow oil. $\delta_H$ (400 MHz, $CDCl_3$) 1.19 (t, 6H, $J$ = 7.1 Hz), 1.33 (t, 3H, $J$ = 7.1 Hz), 3.60 (q, 2H, $J$ = 7.1 Hz), 3.60 (q, 2H, $J$ = 7.1 Hz), 3.67 (q, 2H, $J$ = 7.1 Hz), 4.35 (q, 2H, $J$ = 7.1 Hz), 5.64 (s, 1H), 8.14 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 15.0 (2C), 61.4, 62.7 (2C), 98.8, 128.4, 147.0, 161.4, 170.2. Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61. Found: C, 50.78; H, 6.72.

**2-(Diethoxymethyl)thiazole-4-carboxamide 11.** A solution of **9** (6 g, 23.2 mmol) in methanol (60 mL) was saturated with ammonia (ca. 7% p/v). The resulting solution was stirred at ambient temperature for 24 h. The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 50:50) to give pure **11** (3.05 g, 57%) as a white solid. Mp 112−114 °C. $\delta_H$ (400 MHz, DMSO-$d_6$) 1.16 (t, 6H, $J$ = 7.1 Hz), 3.65 (bq, 4H, $J$ = 7.1 Hz), 5.71 (s, 1H), 7.59 (bs, 1H), 7.70 (bs, 1H), 8.28 (s, 1H). $\delta_C$ (100 MHz, DMSO-$d_6$) 15.1, 61.8, 97.7, 125.0, 150.5, 162.1, 168.7. Anal. Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13. Found: C, 47.11; H, 6.27.

**Ethyl-2-formylthiazole-4-carboxylate 10.** To a solution of 2.70 g of **9** (10.4 mmol) in acetone (100 mL) was added 1 M hydrochloric acid (10 mL). The resulting solution was refluxed for 1 h. The solution was then partially evaporated and treated with EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (3 × 25 mL) and brine (3 × 20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The obtained crude aldehyde was used in the next step without purification. $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (t, 3H, $J$ = 7.1 Hz), 4.42 (q, 2H, $J$ = 7.1 Hz), 8.45 (s, 1H), 10.01 (s, 1H).

**2-Formylthiazole-4-carboxamide 12.** The same procedure described above for the transformation of **9** into **10** was applied to **11** (3.01 g, 13.1 mmol). The crude aldehyde **13** was used in the next step without further purification. $\delta_H$ (400 MHz, DMSO-$d_6$) 7.74 (bs, 1H), 7.96 (bs, 1H), 8.26 (s, 1H), 9.90 (s, 1H).

***N*-Benzyl-*C*-[4-(ethoxycarbonyl)-2-thiazolyl)] Nitrone 5a.** A solution of **10** (obtained from 10.4 mmol of **9**) in $CH_2Cl_2$ (30 mL) was treated sequentially with $MgSO_4$ (1 g) and *N*-benzylhydroxylamine (1.28 g, 10.4 mmol). The resulting mixture was stirred at ambient temperature for 6 h, at which time the reaction mixture was filtered and the residue was washed with $CH_2Cl_2$ (5 × 20 mL). The combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography (gradient hexane/EtOAC 60:40 to EtOAc 100%) to give nitrone **5a** (2.17 g, 72% from **9**) as a white solid. Mp 164−166 °C. $\delta_H$ (400 MHz, $CDCl_3$) 1.32 (t, 3H, $J$ = 7.0 Hz), 4.36 (q, 2H, $J$ = 7.0 Hz), 5.1 (s, 2H), 7.4 (s, 5H), 8.11 (s, 1H), 8.15 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.3, 61.6, 69.6, 127.6, 129.3, 129.7, 130.0, 130.3, 131.2, 147.6, 157.0, 161.3. Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 58.13; H, 4.99; N, 9.42.

***N*-Benzyl-*C*-[4-(aminocarbonyl)-2-thiazolyl)] Nitrone 5b.** The same procedure described above for the transformation of **10** into **5a** was applied to **12** (obtained from 13.1 mmol of **11**). After purification by column chromatography (gradient hexane/EtOAC 20:80 to EtOAc 100%), pure **5b** (2.19 g, 64% from **11**) was obtained as a slightly yellow solid. Mp 198−200 °C (dec). $\delta_H$ (400 MHz, DMSO-$d_6$) 5.32 (s, 2H), 7.38−7.45 (m, 3H), 7.49−7.55 (m, 2H), 7.65 (bs, $1H_a$), 7.75 (bs, 1H), 8.26 (s, 1H), 8.84 (s, 1H). $\delta_C$ (100 MHz, DMSO-$d_6$) 68.0, 123.9, 128.6, 128.7, 129.4, 129.9, 133.6, 150.9, 155.9, 162.3. Anal. Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08. Found: C, 55.34; H, 4.28; N, 15.86.

***N*-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose-1-yl)-*C*-[4-(ethoxycarbonyl)-2-thiazolyl)] Nitrone 5c.** A solution of **10** (obtained from 10.4 mmol of **9**) in $CH_2Cl_2$ (30 mL) was treated sequentially with $MgSO_4$ (1.0 g) and *N*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose-1-yl)hydroxylamine (2.85 g, 4.7 mmol). The resulting mixture was heated at reflux for 3 days, at which time the reaction mixture was filtered and the residue was washed with $CH_2Cl_2$ (5 × 20 mL). The combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAC 60:40) to give nitrone **5c** (2.81 g, 61% from **9**) as a white solid. Mp 169−171 °C. $[\alpha]_D$ +42 (*c* 0.88, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 1.30 (s, 3H), 1.32 (s, 3H), 1.36 (t, 3H, $J$ = 7.1 Hz), 1.39 (s, 3H), 1.47 (s, $3H_3$), 4.03−4.09 (m, 2H), 4.37 (ddd, 1H, $J$ = 0.8, 5.8, 6.8 Hz), 4.40 (q, 2H, $J$ = 7.1 Hz), 4.44 (dd, 1H, $J$ = 3.5, 6.8 Hz), 4.88 (dd, 1H, $J$ = 3.5, 5.8 Hz), 5.27 (d, 1H, $J$ = 5.8 Hz), 5.51 (s, 1H), 8.22 (s, 1H), 8.47 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 24.4, 25.1, 26.0, 26.8, 61.8, 66.3, 73.0, 79.8, 84.5, 85.2, 102.5, 109.4, 113.7, 128.1, 128.6, 148.0, 156.0, 161.3. Anal. Calcd for $C_{19}H_{26}N_2O_8S$: C, 51.57; H, 5.92; N, 6.33. Found: C, 51.76; H, 6.17; N, 6.14.

**Cycloaddition Reactions between Nitrones 5 and Allylic Alcohol. In the Absence of a Lewis Acid.** A solution of the corresponding nitrone **5** (3.4 mmol) in $CH_2Cl_2$ (100 mL) was treated with allylic alcohol (12 mL, 176 mmol) at ambient temperature. The reaction mixture was heated at 70 °C in a sealed tube until no more starting material was observed (TLC). After being cooled at ambient temperature, the reaction mixture was treated with brine (100 mL). The organic layer

was separated, washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was purified by column chromatography (hexane/EtOAc, 60:40).

**In the Presence of a Lewis Acid.** A solution of the corresponding nitrone **5** (3.4 mmol) in $CH_2Cl_2$ (100 mL) was treated with 1.0 equiv of Lewis acid (3.4 mmol) at ambient temperature, and the resulting mixture was stirred for 15 min, at which time allylic alcohol (12 mL, 176 mmol) was added. The reaction mixture was heated at 70 °C in a sealed tube until no more starting material was observed (TLC). After being cooled at ambient temperature, the reaction mixture was treated with a saturated aq solution of EDTA (100 mL). The organic layer was separated, washed with brine (2 × 50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which is purified by column chromatography (hexane/EtOAc, 80:20).

**Under Microwave Irradiation and in the Presence of Lewis Acids (Only for Nitrone 5a).** To a pressure tube containing 2 mL of anhydrous $CH_2Cl_2$ were added 0.1 g (0.34 mmol) of nitrone **5a** and 0.12 g (0.34 mmol) of $Zn(OTf)_2$. The resulting suspension was stirred for 15 min, then 1.2 mL (1.76 mmol) of allylic alcohol was added, and the mixture was inserted into the cavity of a microwave apparatus and heated at 90 W for 15 min (internal temperature 120 °C). After being cooled at room temperature, the reaction mixture was treated with a saturated aqueous solution of Na−EDTA (10 mL). The organic layer was separated, washed with brine (2 × 5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which is purified by flash chromatography (hexane/EtOAc 80:20) to give **14** (64 mg, 54%) and **17** (44 mg, 36%) as the only products of the reaction (see Table 1, entry 6).

**Ethyl 2-((3*S**,5*R**)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-3-yl)thiazole-4-carboxylate 14.** Oil. $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (t, 3H, $J$ = 7.0 Hz), 2.22 (bs, 1H), 2.49 (td, 1H, $J$ = 5.4, 13.1 Hz), 2.97 (td, 1H, $J$ = 8.6, 13.1 Hz), 3.55 (dd, 1H, $J$ = 5.5, 11.8 Hz), 3.66 (dd, 1H, $J$ = 2.2, 11.8 Hz), 4.00 (d, 1H, $J$ = 13.4 Hz), 4.08 (d, 1H, $J$ = 13.4 Hz), 4.39 (q, 2H, $J$ = 7.0 Hz), 4.47 (dtd, 1H, $J$ = 2.9, 5.5, 8.5 Hz), 4.53 (dd, 1H, $J$ = 5.4, 8.6 Hz), 7.23−7.40 (m, 5H), 8.10 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.3, 37.6, 60.4, 61.0, 64.0, 66.8, 78.6, 127.9, 128.1, 128.6, 129.2, 137.3, 147.9, 161.4, 173.7. Anal. Calcd for $C_{17}H_{20}N_4O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.49; H, 5.90; N, 8.24.

**Ethyl 2-((3*S**,5*S**)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-3-yl)thiazole-4-carboxylate 17.** Oil. $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (t, 3H, $J$ = 7.1 Hz), 2.26 (bs, 1H), 2.56 (ddd, 1H, $J$ = 4.4, 7.4, 12.5 Hz), 2.72 (td, 1H, $J$ = 8.1, 12.5 Hz), 3.59 (dd, 1H, $J$ = 4.4, 12.1 Hz), 3.80 (dd, 1H, $J$ = 2.9, 12.1 Hz), 4.01 (d, 1H, $J$ = 13.6 Hz), 4.08 (d, 1H, $J$ = 13.6 Hz), 4.22 (ddt, 1H, $J$ = 2.9, 4.4, 7.7 Hz), 4.40 (q, 2H, $J$ = 7.1 Hz), 4.52 (dd, 1H, $J$ = 4.4, 8.1 Hz), 7.24−7.40 (m, 5H), 8.12 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.3, 37.8, 61.3, 61.5, 62.8, 66.5, 78.5, 127.6, 128.3, 128.4, 128.8, 136.3, 147.2, 161.3, 173.1. Anal. Calcd for $C_{17}H_{20}N_4O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.83; H, 5.95; N, 7.88.

***N*-Benzyl-*C*-[4-(allyloxycarbonyl)-2-thiazolyl)] Nitrone 16.** White solid. Mp 136−138 °C. $\delta_H$ (400 MHz, $CDCl_3$) 4.81 (ddd, 2H, $J$ = 1.1, 1.5, 5.9 Hz), 5.12 (s, 2H), 5.25 (td, 1H, $J$ = 1.3, 10.3 Hz), 5.35 (dq, 1H, $J$ = 1.5, 17.3 Hz), 5.98 (tdd, 1H, $J$ = 5.9, 10.3, 17.3 Hz), 7.40 (s, 5H), 8.12 (s, 1H), 8.20 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 66.1, 69.6, 119.1, 127.8, 129.3, 129.7, 129.9, 130.3, 131.1, 131.6, 147.2, 157.0, 161.0. Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.43; H, 4.51; N, 9.66.

**Allyl 2-((3*S**,5*R**)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-3-yl)thiazole-4-carboxylate 17.** Oil. $\delta_H$ (400 MHz, $CDCl_3$) 2.16 (bs, 1H), 2.50 (td, 1H, $J$ = 5.1, 12.8 Hz), 2.98 (td, 1H, $J$ = 8.6, 12.8 Hz), 3.52−3.71 (m, 2H), 4.01 (d, 1H, $J$ = 13.4 Hz), 4.10 (d, 1H, $J$ = 13.4 Hz), 4.45−4.51 (m, 1H), 4.53 (dd, 1H, $J$ = 5.1, 8.6 Hz), 4.83 (ddd, 2H, $J$ = 1.0, 1.3, 6.1 Hz), 5.28 (tdd, 1H, $J$ = 1.0, 1.3, 10.2 Hz), 5.39 (tdd, 1H, $J$ = 1.0, 1.3, 17.2 Hz), 6.02 (tdd, 1H, $J$ = 6.1, 10.2, 17.2 Hz), 7.23−7.41 (m, 5H), 8.13 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 37.5, 60.4, 63.9, 65.5, 66.7, 78.5, 118.1, 128.3, 128.5, 128.6, 129.2, 132.6, 137.3, 147.5, 160.9, 173.8. Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 59.71; H, 5.47; N, 7.52.

***N*-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose-1-yl)-*C*-[4-(allyloxycarbonyl)-2-thiazolyl)] Nitrone 18.** Mp 146−148 °C; $[\alpha]_D$ +27 (*c* 0.70, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.34 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 4.07−4.13 (m, 2H), 4.41 (ddd, 1H, $J$ = 4.4, 5.5, 7.0 Hz), 4.48 (dd, 1H, $J$ = 3.7, 7.0 Hz), 4.87 (ddd, 2H, $J$ = 1.1, 1.5, 5.9 Hz), 4.92 (dd, 1H, $J$ = 3.7, 5.9 Hz), 5.29 (tdd, 1H, $J$ = 1.1, 1.5, 10.3 Hz), 5.31 (d, 1H, $J$ = 5.9 Hz), 5.40 (qd, 1H, $J$ = 1.5, 17.3 Hz), 5.56 (s, 1H), 6.03 (tdd, 1H, $J$ = 5.9, 10.3, 17.3 Hz), 8.28 (s, 1H), 8.51 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 24.3, 25.0, 25.9, 26.7, 66.2(×2), 73.0, 79.8, 84.4, 85.2, 102.5, 109.3, 113.7, 119.2, 128.3, 128.5, 131.6, 147.6, 156.0, 160.1. Anal. Calcd for $C_{20}H_{26}N_2O_8S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.64; H, 5.55; N, 6.01.

***N*-(2,3-*O*-Isopropylidene-α-D-mannofuranose-1-yl)-*C*-[4-(allyloxycarbonyl)-2-thiazolyl)] Nitrone 19.** Mp 150−152 °C; $[\alpha]_D$ +31 (*c* 0.70, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.36 (s, $3H_3$), 1.53 (s, 3H), 2.98 (bs, 2H), 3.81 (dd, 1H, $J$ = 5.1, 11.4 Hz), 3.90 (dd, 1H, $J$ = 3.3, 11.4 Hz), 4.00−4.11 (m, 1H), 4.47 (dd, 1H, $J$ = 4.0, 8.5 Hz), 4.86 (ddd, 2H, $J$ = 1.1, 1.5, 5.9 Hz), 5.01 (dd, 1H, $J$ = 4.0, 5.9 Hz), 5.30 (tdd, 1H, $J$ = 1.1, 1.5, 10.3 Hz), 5.31 (d, 1H, $J$ = 5.9 Hz), 5.40 (qd, 1H, $J$ = 1.5, 17.0 Hz), 5.58 (s, 1H), 6.02 (tdd, 1H, $J$ = 5.9, 10.3, 17.0 Hz), 8.27 (s, 1H), 8.56 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 24.7, 26.1, 63.7, 66.3, 70.1, 80.4, 83.9, 84.4, 102.4, 113.8, 119.3, 128.4, 128.5, 131.6, 147.5, 156.2, 160.9. Anal. Calcd for $C_{17}H_{27}N_2O_8S$: C, 49.27; H, 5.35; N, 6.76. Found: C, 49.47; H, 5.16; N, 6.96.

**Ethyl 2-[2-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose-1-yl)-5-(hydroxymethyl)isoxazolidin-3-yl]thiazole-4-carboxylate 21.** (Selected signals) $\delta_H$ (400 MHz, $CDCl_3$) 1.30 (s, 3H), 1.32 (s, 3H), 1.34 (s, 6H), 1.35 (t, 3H, $J$ = 7.0 Hz), 1.45 (s, 1H), 2.70 (ddd, 1H, $J$ = 3.7, 6.6, 13.2 Hz), 2.83 (td, 1H, $J$ = 8.8, 13.2 Hz), 3.46 (dd, 1H, $J$ = 5.1, 12.5 Hz), 3.66 (dd, 1H, $J$ = 2.9, 12.5 Hz), 3.77 (dd, 1H, $J$ = 4.4, 8.5 Hz), 3.98 (dd, 1H, $J$ = 6.2, 8.5 Hz), 4.09 (dd, 1H, $J$ = 3.7, 7.0 Hz), 4.28−4.41 (m, 1H), 4.36 (q, 2H, $J$ = 7.0 Hz), 4.44−4.53 (m, 1H), 4.56 (s, 1H), 4.83 (dd, 1H, $J$ = 3.7, 5.9 Hz), 4.89 (dd, 1H, $J$ = 3.7, 8.8 Hz), 5.02 (d, 1H, $J$ = 5.9 Hz), 8.05 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.3, 24.5, 25.1, 26.0, 26.8, 35.9, 61.5, 63.0, 63.2, 66.6, 73.0, 80.0, 80.2, 82.8, 83.9, 96.6, 109.2, 112.8, 127.9, 147.4, 161.3, 174.2.

**Ethyl 2-{(3*S*,5*R*)-2-Benzyl-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidin-3-yl}thiazole-4-carboxylate 23 and Ethyl 2-{(3*R*,5*R*)-2-Benzyl-5-[(4*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidin-3-yl}thiazole-4-carboxylate 24.** A solution of nitrone **5a** (1.46 g, 5 mmol) in toluene (100 mL) was treated with vinyl dioxolane (1.3 g, 10 mmol) at ambient temperature. The resulting solution was heated at 140 °C for 12 days in a sealed tube and under an argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was purified by radial chromatography (hexane/EtOAc, 80:20) to afford recovered starting nitrone **5a** (0.88 g, 60%) and pure **23** and **24**.

**23.** (0.316 g, 18%). Oil; $[\alpha]_D$ +66 (*c* 0.70, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.28 (s, 3H, $CH_3$), 1.33 (s, 3H), 1.39 (t, 3H, $J$ = 7.1 Hz), 2.67 (ddd, 1H, $J$ = 5.0, 5.3, 13.4 Hz), 3.05 (td, 1H, $J$ = 8.3, 13.4 Hz), 3.76 (m, 1H), 3.95−4.02 (m, 3H), 4.12 (d, 1H, $J$ = 13.4 Hz), 4.30 (m, 1H), 4.40 (q, 2H, $J$ = 7.1 Hz), 4.55 (dd, 1H, $J$ = 5.0, 8.6 Hz), 7.24−7.39 (m, 5H), 8.10 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 25.2, 26.7, 39.4, 60.6, 61.4, 66.4, 67.3, 76.9, 78.7, 109.5, 127.7, 128.2, 128.5, 128.9, 136.3, 147.2, 161.4, 174.1. Anal. Calcd for $C_{21}H_{26}N_2O_5S$: C, 60.27; H, 6.26; N, 6.69. Found: C, 60.14; H, 6.00; N, 6.83.

**24.** (0.209 g, 10%). Oil; $[\alpha]_D$ −46 (*c* 0.70, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.36 (s, 3H), 1.40 (t, 3H, $J$ = 7.1 Hz), 1.41 (s, 3H), 2.72 (ddd, 1H, $J$ = 4.8, 7.3, 12.9 Hz), 2.78 (td, 1H, $J$ = 7.8, 12.9 Hz), 3.75 (dd, 1H, $J$ = 5.8, 8.6 Hz), 3.98 (d, 1H, $J$ = 13.4 Hz), 4.03−4.08 (m, 2H), 4.11 (d, 1H, $J$ = 13.0 Hz), 4.15

(dd, 1H, $J$ = 6.3, 12.4 Hz), 4.42 (q, 2H, $J$ = 7.1 Hz), 4.56 (dd, 1H, $J$ = 4.8, 7.8 Hz), 7.23−7.38 (m, 5H), 8.13 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 25.2, 26.5, 38.7, 53.4, 61.5, 68.4, 67.3, 76.8, 79.1, 109.8, 127.7, 128.4, 128.5, 129.0, 136.4, 147.2, 161.4, 173.2. Anal. Calcd for $C_{21}H_{26}N_2O_5S$: C, 60.27; H, 6.26; N, 6.69. Found: C, 60.39; H, 6.17; N, 6.54.

**Cycloaddition Reaction between Nitrone 5a and (2*S*)-1,2-Dihydroxy-1-butene 25.** To a pressure tube containing 4 mL of 1:1 $CH_2Cl_2$:EtOH was added 0.2 g (0.68 mmol) of nitrone **5a**. The resulting solution was treated with 0.182 g (2.06 mmol) of (2*S*)-1,2-hydroxybutene **25**, and the resulting mixture was inserted into the cavity of a microwave apparatus and heated at 90 W for 1 h (internal temperature 120 °C). After being cooled at room temperature, the reaction mixture was treated with brine (5 mL). The organic layer was separated, washed with brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography (hexane/EtOAc 70:30) to give the pure compounds **27** (see Table 2, entry 2) in 60% total yield.

**Ethyl 2-{(3*R*,5*S*)-2-Benzyl-5-[(2*R*)-1,2-dihydroxy-2-ethyl]isoxazolidin-3-yl}thiazole-4-carboxylate 27a.** (30 mg, 10%). Oil; $[\alpha]_D$ −86 (*c* 0.56, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.34 (t, 3H, $J$ = 7.1 Hz), 2.18 (bs, 2H), 2.50 (dt, 1H, $J$ = 5.6, 12.2 Hz), 2.91 (dt, 1H, $J$ = 8.6, 12.2 Hz), 3.50 (dd, 1H, $J$ = 6.6, 12.4 Hz), 3.55−3.60 (m, 2H), 3.95 (s, 2H), 4.34 (q, 2H, $J$ = 7.1 Hz), 4.37 (m, 1H), 4.47 (dd, 1H, $J$ = 5.8, 8.4 Hz), 7.22−7.31 (m, 5H), 8.06 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 38.8, 60.6, 61.5, 63.8, 66.8, 73.2, 78.2, 127.8, 128.2, 128.6, 128.8, 136.2, 147.2, 161.2, 172.6. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.32; H, 5.74; N, 7.28.

**Ethyl 2-{(3*S*,5*R*)-2-Benzyl-5-[(2*R*)-1,2-dihydroxy-2-ethyl]isoxazolidin-3-yl}thiazole-4-carboxylate 27b.** (30 mg, 10%). Oil; $[\alpha]_D$ +52 (*c* 0.38, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.32 (t, 3H, $J$ = 7.1 Hz), 2.40 (bs, 2H), 2.70 (dt, 1H, $J$ = 5.6, 13.2 Hz), 2.90 (dt, 1H, $J$ = 8.6, 13.2 Hz), 3.49 (dd, 1H, $J$ = 5.8, 11.6 Hz), 3.58 (dd, 1H, $J$ = 3.5, 11.6 Hz), 3.66 (q, 1H, $J$ = 5.1 Hz), 3.90 (d, 1H, $J$ = 13.2 Hz), 4.01 (d, 1H, $J$ = 13.2 Hz), 4.32 (q, 2H, $J$ = 7.1 Hz), 4.36 (m, 1H), 4.46 (dd, 1H, $J$ = 4.8, 8.4 Hz), 7.20−7.31 (m, 5H), 8.03 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 37.0, 60.5, 61.4, 63.6, 67.6, 72.2, 79.1, 127.8, 128.2, 128.7, 129.0, 136.1, 147.2, 161.2, 171.3. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.04; H, 5.79; N, 7.60.

**Ethyl 2-{(3*S*,5*S*)-2-Benzyl-5-[(2*R*)-1,2-dihydroxy-2-ethyl]isoxazolidin-3-yl}thiazole-4-carboxylate 27c.** (60 mg, 20%). Oil; $[\alpha]_D$ −70 (*c* 0.32, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.33 (t, 3H, $J$ = 7.3 Hz), 2.00 (bs, 2H), 2.55 (ddd, 1H, $J$ = 4.5, 7.0, 12.3 Hz), 2.75 (dt, 1H, $J$ = 8.6, 12.3 Hz), 3.49 (dd, 1H, $J$ = 6.6, 11.6 Hz), 3.62 (dd, 1H, $J$ = 3.3, 11.6 Hz), 3.81 (m, 1H), 3.94 (d, 1H, $J$ = 13.4 Hz), 4.00 (d, 1H, $J$ = 13.4 Hz), 4.02 (m, 1H), 4.34 (q, 2H, $J$ = 7.3 Hz), 4.46 (m, 1H), 7.20−7.32 (m, 5H), 8.06 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.4, 37.4, 60.8, 61.4, 63.7, 66.5, 72.0, 78.9, 127.7, 128.0, 128.6, 129.0, 136.2, 147.0, 161.3, 172.5. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.35; H, 5.93; N, 7.58.

**Ethyl 2-{(3*S*,5*R*)-2-Benzyl-5-[(2*R*)-1,2-dihydroxy-2-ethyl]isoxazolidin-3-yl}thiazole-4 carboxylate 27d.** (60 mg, 20%). Oil; $[\alpha]_D$ +59 (*c* 0.496, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 1.33 (t, 3H, $J$ = 7.1 Hz), 2.15 (bs, 2H), 2.64 (ddd, 1H, $J$ = 3.8, 6.6, 12.2 Hz), 2.75 (dt, 1H, $J$ = 8.4, 12.2 Hz), 3.55−365 (m, 3H), 3.95 (d, 1H, $J$ = 13.2 Hz), 3.97 (m, 1H), 4.05 (d, 1H, $J$ = 13.2 Hz), 4.35 (q, 2H, $J$ = 7.1 Hz), 4.51 (m, 1H), 7.20−7.32 (m, 5H), 8.06 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 14.5, 37.9, 61.6 (2C), 64.5, 66.2, 72.9, 79.7, 127.8, 128.5, 128.6, 128.9, 136.2, 147.3, 161.5, 171.4. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 56.93; H, 5.96; N, 7.21.

**Ethyl 2-{(3*R*,5*S*)-2-Benzyl-5-[(2*R*)-1-(*tert*-butyldiphenylsiloxy)-2-ethyl]isoxazolidin-3-yl}thiazole-4-carboxylate 28a and Ethyl 2-{(3*S*,5*R*)-2-Benzyl-5-[(2*R*)-1-(*tert*-butyldiphenylsiloxy)-2-hydroxy-2-ethyl]isoxazolidin-3-yl}-thiazole-4-carboxylate 28b.** To a pressure tube containing 2 mL of anhydrous $CH_2Cl_2$ were added 0.1 g (0.34 mmol) of nitrone **5a** and 0.12 g (0.34 mmol) of $Zn(OTf)_2$. The resulting suspension was stirred for 15 min, then 0.34 g (1.03 mmol) of (2*S*)-1-*O*-(*tert*-butyldiphenylsylyl)-3-butene-1,2-diol **26**[22] was added, and the mixture was inserted into the cavity of a microwave apparatus and heated at 90 W for 2 h (internal temperature 120 °C). After being cooled at room temperature, the reaction mixture was treated with a saturated aqueous solution of Na−EDTA (10 mL). The organic layer was separated, washed with brine (2 × 5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography (hexane/EtOAc 80:20) to give pure **28a** and **28b**.

**28a.** (0.117 g, 56%). Oil; $[\alpha]_D$ −53 (*c* 0.29, $CHCl_3$). $\delta_H$ (500 MHz, $CDCl_3$) 0.96 (9H, s), 1.32 (t, 3H, $J$ = 7.0 Hz), 2.45 (dt, 1H, $J$ = 6.0, 12.5 Hz), 2.63 (bs, 1H), 2.90 (dt, 1H, $J$ = 5.0, 12.5 Hz), 3.59 (m, 3H), 3.92 (d, 1H, $J$ = 13.5 Hz), 3.97 (d, 1H, $J$ = 13.5 Hz), 4.33 (q, 2H, $J$ = 7.0 Hz), 4.44 (dd, 1H, $J$ = 6.0, 8.5 Hz), 4.49 (dd, 1H, $J$ = 5.0, 9.0 Hz), 7.17−7.35 (m, 10H), 7.54−7.59 (m, 4H), 8.02 (s, 1H). $\delta_c$ (200 MHz, $CDCl_3$) 14.3, 19.2, 26.8, 38.9, 60.4, 61,4, 64.6, 66.8, 73.3, 77.3, 127.7, 128.1, 128.4, 128.7, 129.7, 133.1, 135.5, 136.2, 147.08, 161.2, 172.8. Anal. Calcd for $C_{34}H_{40}N_2O_5SSi$: C, 66.20; H, 6.54; N, 4.54. Found: C, 66.47; H, 6.20; N, 4.80.

**28b.** (30 mg, 14%). Oil; $[\alpha]_D$ +22 (*c* 0.3, $CHCl_3$). $\delta_H$ (500 MHz, $CDCl_3$) 0.97 (s, 9H), 1.32 (t, 3H, $J$ = 7.5 Hz), 1.59 (bs, 1H), 2.61 (dt, 1H, $J$ = 12.0, 5.5 Hz), 2.85 (dt, 1H, $J$ = 12.0, 8.0 Hz), 3.57 (dd, 1H, $J$ = 5.0, 10.0 Hz), 3.62 (dd, 1H, $J$ = 8.0, 10.0 Hz), 3.69 (m, 1H), 3.90 (d, 1H, $J$ = 13.0 Hz), 3.96 (d, 1H, $J$ = 13.0 Hz), 4.33 (q, 2H, $J$ = 7.5 Hz), 4.37 (ddd, 1H, $J$ = 3.5, 5.5, 8.5 Hz), 4.44 (dd, 1H, $J$ = 5.5, 9.0 Hz), 7.15−7.36 (m, 10H), 7.53−7.56 (m, 4H), 8.07 (s, 1H). Anal. Calcd for $C_{34}H_{40}N_2O_5SSi$: C, 66.20; H, 6.54; N, 4.54. Found: C, 66.27; H, 6.48; N, 4.54.

**Desilylation of 28a and 28b.** A solution of **28a** (0.1 g, 0.162 mmol) in THF (20 mL) was treated with anhydrous $Bu_4NF$ in THF (2 mL of a 1.0 M solution, 2 mmol). The resulting solution was stirred at ambient temperature for 3 h, at which time the reaction mixture was partitioned between brine (20 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 50:50) to afford pure **27a** (55 mg, 90%).

The same procedure was applied to **28b** (0.1 g, 0.162 mmol). After purification, pure **27b** was obtained (54 mg, 88%).

These compounds showed physical and spectroscopic properties identical to those obtained from the cycloaddition between **5a** and **24**.

**2-[(3*S*,5*R*)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-3-yl]thiazole-4-carboxamide 4 (Isoxazolidine Analogue of Tiazofurin). From 14 (Synthesis of (±)-4).** A solution of **14** (0.4 g, 1.14 mmol) in methanol (30 mL) was saturated with ammonia (ca 7% p/v). The resulting solution was stirred at ambient temperature for 24 h. The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to give pure (±)-**4** (0.37 g, quant.) as a sticky foam.

**From 27a (Synthesis of (−)-4).** A cooled (to 0 °C) solution of **27a** (76 mg, 0.2 mmol) in a 1:1 mixture of MeOH:$H_2O$ (10 mL) was treated with $NaIO_4$ (42 mg, 0.2 mmol). The resulting suspension was stirred at 0 °C for 1 h, filtered, and rotatory evaporated. The residue was taken up in aqueous methanol (8 mL), cooled to 0 °C, and treated with $NaBH_4$ (24 mg, 0.6 mmol). After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 80:20) on silica gel to give pure (−)-**14** (56 mg, 80%; $[\alpha]_D$ −54 (*c* 0.38, $CHCl_3$)). The same procedure described above was then applied to **14**. After purification by radial chromatography (EtOAc), enantiomerically pure **4** (52 mg, 80% from **27a**) was obtained.

**(−)-4.** Oil; $[\alpha]_D$ −73 (*c* 0.45, $CHCl_3$). $\delta_H$ (400 MHz, $CDCl_3$) 2.49 (ddd, 1H, $J$ = 5.0, 5.6, 12.6 Hz), 2.73 (bs, 1H), 2.84 (ddd, 1H, $J$ = 8.3, 8.6, 12.6 Hz), 3.49 (dd, 1H, $J$ = 5.6, 11.9 Hz), 3.58 (dd, 1H, $J$ = 2.8, 11.9 Hz), 3.93 (d, 1H, $J$ = 13.4 Hz), 4.05 (d, 1H, $J$ = 13.4 Hz), 4.35 (dd, 1H, $J$ = 4.5, 8.6 Hz), 4.44 (m, 1H), 6.28 (bs, 1H), 7.02 (bs, 1H), 7.17−7.34 (m, 5H), 7.97 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 37.3, 60.6, 63.6, 66.2, 78.5, 125.3, 127.8, 128.6, 128.9, 136.3, 149.5, 163.3, 173.1. Anal. Calcd for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16. Found: C, 56.21; H, 5.48; N, 13.34.

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