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Synthesis and Configurational Assignment of the Amino Alcohol in the Eastern Fragment of the GE2270 Antibiotics by Regio- and Stereoselective Addition of 2-Metalated 4-Bromothiazoles to α-Chiral Electrophiles

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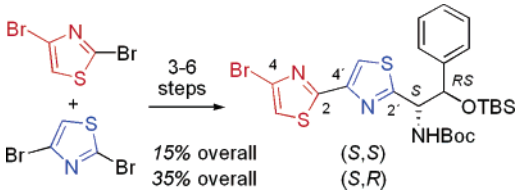
Received March 3, 2006



A synthesis of the eastern fragment of the thiazole peptide GE2270 A (**1**) has been developed. The synthetic approach relies on the regioselective functionalization of 2,4-dibromothiazole (**5**) via metalation and nucleophilic addition (at C2) or palladium-mediated cross-coupling (at C2 or C4). The stereochemistry at the N-bearing stereocenter was established by coupling of 2-metalated 4-bromothiazoles (**4**) to enantiomerically pure mandelic acid derivatives. Both the *erythro* (**2**) and *threo* (**3**) configurated amino alcohols were prepared with high diastereoselectivities depending on the electrophile employed. More specifically, the *threo*-configurated (*S*,*R*)-4-bromothiazolyl *β*-amino alcohol **6** was synthesized from *O*-TBS protected (*R*)-mandelonitrile in 62% yield. Its *N*-PMB protected (*R*,*S*)-enantiomer **20** was obtained from *O*-TBS protected (*S*)-mandelic aldehyde in 67% yield. The *erythro*-configurated (*S*,*S*)-4-bromothiazolyl *β*-amino alcohol **29** was prepared from *O*-TBS protected (*S*)-ethyl mandelate in four steps and 33% overall yield. The bithiazole moiety in the desired products **2** and **3** was finally established by the regioselective Negishi coupling of 2,4-dibromothiazole (**5**) and the 4-zincated, *N*-Boc protected thiazole derivatives of the diastereomeric 4-bromothiazolyl *β*-amino alcohols **6** and **29**.

Introduction

GE2270 A (**1**, Figure 1) is a highly modified macrocyclic peptide that was first isolated in 1991, together with nine other co-metabolites, from the *Planobispora rosea* strain ATCC 53373.[1] It belongs to the family of the thiazole peptides, a novel class of anti-infective natural products produced by actinomycetes which show potent antibacterial activity.[2] Other members of this class of natural products include thiostrepton,[3] micrococcin P,[4] and the amythiamicins.[5] The mechanism of action of GE2270 A is the inhibition of the elongation factor *Tu* (EF-*Tu*; IC_{50} = 5 nM), essential for bacterial protein biosynthesis.[6−8] This biochemical target, previously unexploited

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10.1021/jo060462g CCC: $33.50
Published on Web 05/17/2006

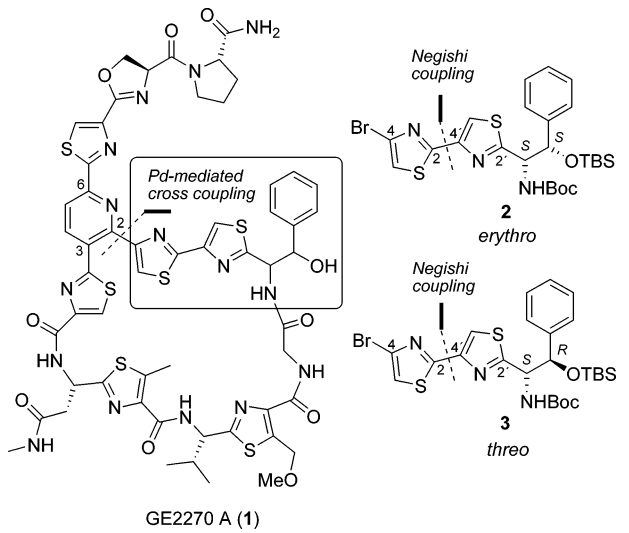

FIGURE 1. Structure of the thiazole peptide GE2270 A and general disconnection strategy for the bithiazole containing eastern fragments (**2** and **3**).

for the clinical development of antibiotics, confers greater importance to this class of natural products. GE2270 A has been the object of an industrial combinatorial chemistry program, aimed at the identification of derivatives of the natural product that retain the biological activity but improve the bioavailability profile.[9]

The general structure of these antibiotics includes a highly substituted nitrogen heterocycle, engaged in a polyazole core that is part of a macrocycle consisting of highly modified amino acid residues. GE2270 A, featuring a trisubstituted pyridine as the central motif, belongs to the series *d* among the thiazolyl peptides, according to Bérdy's classification.[10] The initially proposed structure of the GE2270 factors was revised in 1995,[11] resulting in the thiazole amino acid sequence depicted in Figure 1 (TBS = *tert*-butyldimethylsilyl, Boc = *N*-*tert*-butyloxycarbonyl). The stereochemistry of four of the six stereogenic centers was believed to originate from naturally occurring amino acids. The configurational assignment of the amino alcohol moiety present in the eastern part of the molecule was not addressed until recently, by means of chemical synthesis[12] of a degradation product earlier obtained by Tavecchia et al.[11] Confirmation of the stereostructure proposed for **1** by total synthesis has not yet been possible. The Shin group has reported the synthesis of an advanced linear precursor of GE2270 A, exploiting a strategy that relies on the construction of the heterocyclic core making extensive use of the classical Hantzsch thiazole synthesis.[13] The total synthesis of the structurally related thiazole peptide amythiamicin D was reported by the Moody group, employing a proposed biosynthesis-inspired hetero-Diels−Alder for the construction of the trisubstituted pyridine core.[14] Total syntheses and synthetic approaches toward micrococcin P[15−17] and thiostrepton[18,19] have been reported.

Our general approach for the construction of the heterocyclic core of GE2270 A involves three sequential and regioselective cross-couplings starting from a polyhalogenated pyridine. At the onset of this project it was envisioned that the functional group tolerance of the Pd-mediated cross-coupling methodology should allow the direct introduction of complex thiazole fragments to the pyridine ring.[20] For instance, disconnection at the 2-position of the pyridine reveals our eastern bithiazole building block, depicted in Figure 1 in two possible diastereomeric forms **2** (*erythro*) and **3** (*threo*). The bromine at the 4-position of the 2,4′-bithiazole is expected to undergo a facile metal−bromine exchange necessary for the final Pd-mediated C−C bond forming reaction. The bithiazole moiety can be further disconnected across the 2−4′ bond, according to our previously reported strategy.[21]

Herein we report the synthesis of the GE2270 A amino alcohol fragment (**2**) in enantiomerically pure form, displaying the *erythro* relative configuration, together with its epimer at the carbinol stereocenter (**3**). Previously reported work from our group described the preparation of the eastern bithiazole subunit in both relative configurations, albeit with modest levels of diastereocontrol, starting from (*R*)-mandelonitrile.[22] This material could be transformed into a degradation fragment, unambiguously establishing the stereochemistry of the natural product as *erythro*-(*S*,*S*).[12] However, the development of a method allowing for the stereoselective preparation of either the *threo* or the *erythro* 2-thiazolyl amino alcohol moiety still remained a challenge. The strategy herein described employs

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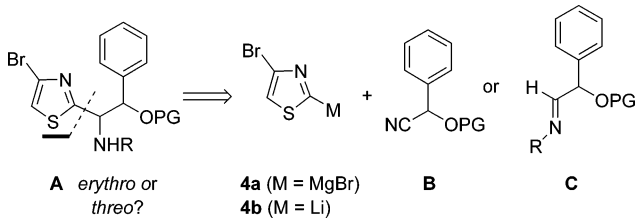
SCHEME 1

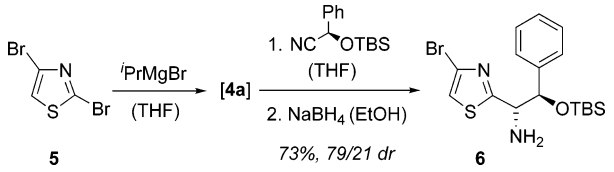


preformed thiazole subunits that can be directly assembled by regioselective metalation and subsequent coupling reactions.

Results and Discussion

Synthetic Strategy. Directly linked bithiazoles represent an important class of natural products that can be mainly obtained from microorganism cultures.[23] Their prominent biological profile has resulted in recent advances in the total synthesis of some members of this class of compounds.[13−17,24] The most extended strategy toward the synthesis of 2,4-disubstituted thiazoles relies on the classical Hantzsch cyclization of a suitable precursor.[25,26] We have developed a concise synthetic strategy to this important structural motif that employs 2,4-dibromothiazole (**5**) as the key building block. Our strategy takes advantage of the higher electrophilicity of the 2-position, a feature that can be exploited in regioselective cross-coupling reactions[27] with a range of organometallic reagents.[28−31] We have also shown that a bromine−metal exchange operation, followed by an electrophilic quench proceeds with total regiocontrol.[22] For the synthesis of the GE2270 A eastern fragment **2**, the required 4-bromothiazole **A** displays a stereogenic center at the α−carbon of the 2-substituent, adding a stereochemical demand to the synthetic process. We envisioned that the nucleophilic addition of a 4-bromo-2-metalated thiazole **4** to a suitable α−chiral nitrogen electrophile could serve to stereoselectively construct the amino alcohol moiety (Scheme 1, PG = protecting group). While the use of an imine **C** should lead directly to the required amino alcohol, the use of a protected mandelonitrile (**B**) requires a further reduction step. In both processes, the coordinating ability of the heterocyclic moiety with metal or organometallic species was expected to play an important role.

SCHEME 2



2-Thiazolyl Addition to *O*-TBS Protected Mandelonitrile and in Situ Reduction. Owing to their utility as latent formyl group equivalents, the synthesis and reactivity of thiazole derivatives has received much attention in the past two decades.[32] The initial operation in the "thiazole−aldehyde synthesis" involves the *umpolung* of 2-bromothiazole via metal−halogen exchange, followed by quenching with a suitable coupling partner. This reaction has been shown to proceed regioselectively at the 2-position when 2,4-dibromothiazole (**5**)[33] is used as the substrate and *n*-BuLi as the metalating agent.[34,35] We found that complete regioselectivity was also observed in the preparation of organomagnesium reagent **4a** when applying the bromine−magnesium exchange protocol developed by Knochel and co-workers.[36] Grignard compound **4a**[22] displays superior thermal stability relative to the corresponding lithiated thiazole **4b**, being the reagent of choice in the reactions with electrophiles that require ambient temperature.

Following the thiazole addition−reduction strategy outlined in Scheme 1, magnesium compound **4a** was treated with enantiomerically pure TBS-protected (*R*)-mandelonitrile to give an intermediate imine that was reduced in situ with $NaBH_4$ in EtOH/MeOH (Scheme 2).[37] The major product, which was obtained in good yield (62% isolated) and moderate diastereoselectivity (79/21 dr), was assigned as the *O*-TBS-protected *threo*-amino alcohol (vide infra). While the use of *i*-PrMgBr·LiCl did not have any noticeable effect on the yield or diastereoselectivity of the process, the addition of a Lewis acid ($ZnCl_2$, 1.0 equiv) prior to the reduction step led to the corresponding amino alcohols in 68% yield with poor diastereocontrol (53/47 dr).

To elucidate the relative configuration of the products of the thiazolyl addition−reduction sequence, we opted for the preparation of cyclic oxazolidine derivatives of the readily separable racemic *erythro*- and *threo*-products (Scheme 3). Protection of the free amino group of the major isomer as the Boc derivative was followed by desilylation with tetrabutylammonium fluoride (TBAF) in THF to give alcohol *rac*-**8**. Treatment with 2,2-dimethoxypropane (DMP) in CH_2Cl_2 in the presence of catalytic amounts of *p*-toluenesulfonic acid afforded the desired oxazolidine *rac*-**9** in 82% yield after 24 h. Following an identical reaction sequence, the oxazolidine derivative of the minor product *rac*-**12** was prepared in 26% overall yield. For this isomer the cyclization reaction required longer reaction times, suggesting the presence of the bulky phenyl and thiazolyl substituents on the same face of the oxazolidine plane. Analysis

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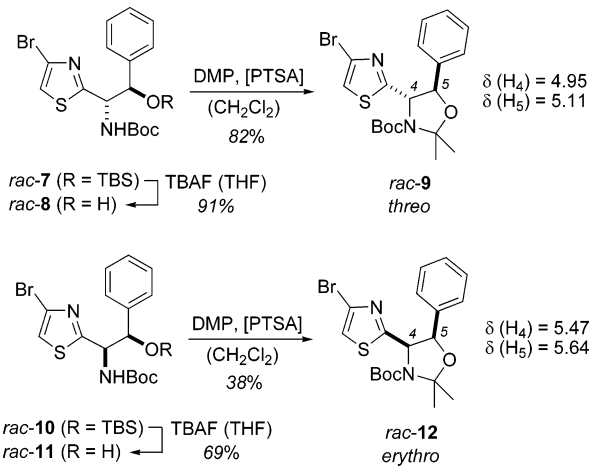
SCHEME 3



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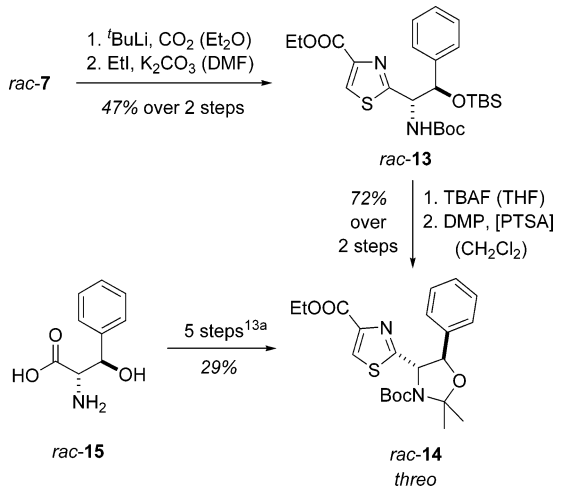

of the chemical shifts in the ^{1}H NMR of the cyclic derivatives *rac*-**9** and *rac*-**12** was used to establish the spatial relationship of the phenyl and thiazolyl substituents.[38] The protons H-4 and H-5 in the *erythro* diastereoisomer resonate at a lower field [$\delta(H_4) = 5.47$, $\delta(H_5) = 5.64$)] with respect to the *threo* compound [($\delta(H_4) = 4.95$, $\delta(H_5) = 5.11$)], due to the anisotropic effect of the phenyl and thiazolyl substituents. These must adopt a perpendicular arrangement to the oxazolidine plane when they are placed *syn* in the cyclic derivative (*rac*-**12**, *erythro*), in order to minimize their steric interaction, leaving H-4 and H-5 under the deshielding effect of their local magnetic fields.

We sought confirmation of our stereochemical assignment through chemical synthesis of a related system. In the realm of their GE2270 A synthetic work, Shin and co-workers described the synthesis of the oxazolidine *rac*-**14** starting from commercially available DL-*threo*-phenylserine (*rac*-**15**) (Scheme 4).[13a] It was noticed that *rac*-**14** could be prepared in a few synthetic operations from our intermediate protected amino alcohol *rac*-**7**. Lithium−bromine exchange followed by the addition of solid carbon dioxide yielded the corresponding 4-thiazolyl carboxylic acid, which was subsequently alkylated with EtI and K_2CO_3 to give *rac*-**13**. For the metalation, it was important to add bromide *rac*-**7** to a *tert*-butyllithium solution

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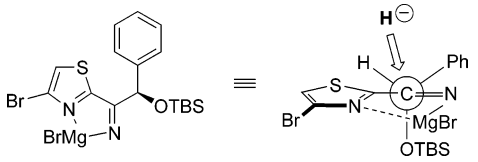


FIGURE 2. Proposed favored conformation of the imine intermediate in the 2-thiazolyl addition−reduction sequence accounting for the observed Felkin−Anh stereocontrol.

in order to avoid formation of the regioisomeric carboxylic acid (vide infra). Following the described silyl deprotection−cyclization sequence (vide supra), we prepared a synthetic material with identical spectroscopical data (^{1}H and ^{13}C NMR) to *rac*-**14**, also synthesized in our laboratories following Shin's route, confirming the determined stereochemistry.

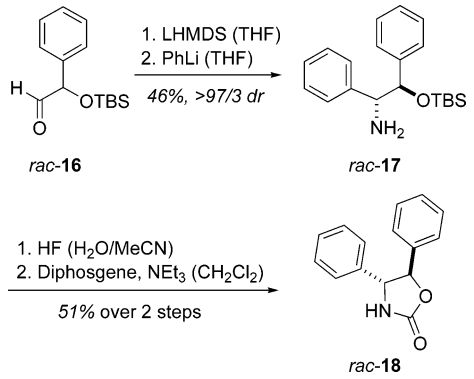
The outcome of the one-pot addition−reduction sequence (Scheme 2) was unexpected, taking into account the existing precedents. Brussee and co-workers have shown that after addition of a range of organomagnesium reagents (RMgBr, where R = Me, Et or Ph) to *O*-TBS protected mandelonitrile the subsequent reduction proceeds with excellent diastereocontrol in all cases to give *erythro* products.[37b] The observed sense of diastereoselection was attributed to a chelation controlled transition state, involving the oxygenated substituent, operating in the imine reduction step. The presence of the thiazole nitrogen could lead to an alternative chelate, in which there is free rotation around the imine−carbinol bond. In the proposed Felkin−Anh transition state,[39] depicted in Figure 2, the silyloxy substituent is placed perpendicular to the imine plane, with the hydride attack occurring from the favored Bürgi−Dunitz trajectory.

Once we had secured the stereochemical assignment of the amino alcohol moiety, our attention turned to the development of a stereoselective method for the preparation of the (*S*,*S*)-*erythro* isomer. The observed sense of 1,2-stereoinduction in the imine reduction step described above suggested that we could possibly reverse the observed diastereoselectivity by modifying the electrophile. We reasoned that the addition of 2-metalated thiazole to a suitable imine derivative should lead to the *erythro* amino alcohol, if a similar Felkin−Anh stereocontrolling pathway remained operative. The required aldimines could be prepared by condensation of the corresponding primary amines with *O*-TBS protected mandelic aldehyde (**16**), which can be readily prepared in enantiomerically pure form from mandelic acid.[40] However, the use of aldimines as electrophilic counterparts entails problems associated with the electrophilic amination of organometallic species, such as the poor electrophilicity of the imino group and the tendency of the α-chiral enolizable imine to undergo deprotonation rather than addition.[41,42]

Attempted 2-Thiazolyl Additions to *N*-Trimethylsilyl Imines. One of the general strategies to increase the electrophilicity of the carbon atom of imines involves the coordination of a Lewis acid with the nitrogen lone pair. This offers the advantage that the activating group does not need to be removed after the nucleophilic addition, a subsequent operation that is not always easily carried out in the case of *N*-alkylated, *N*-sulfonylated, or

(39) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.
(40) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984−5990.
(41) Review: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.
(42) Review: Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.

SCHEME 5



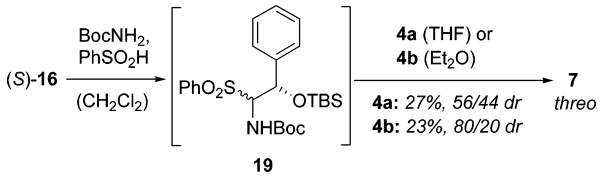
N-oxidized imine derivatives. One particularly convenient method employs *N*-trimethylsilyl aldimines, prepared in situ by treatment of the corresponding aldehyde with lithium bis(trimethylsilyl)amide (LHMDS) at low temperature.[43,44] Although the use of this type of silylated imines is generally restricted to nonenolizable aldimines, we were pleased to discover that the *N*-trimethylsilyl aldimine derivative of the α-chiral aldehyde *rac*-**16** could be quenched with phenyllithium to yield after workup exclusively the *O*-protected amino alcohol *rac*-**17** (Scheme 5).

Disappointingly, the stereochemistry of the product was assigned as *threo* after conversion to the oxazolidinone derivative *rac*-**18**, the spectroscopical data of which (^{1}H and ^{13}C NMR) have been reported for both diastereoisomers.[45,46] In addition, our attempts to couple 2-metalated thiazoles **4a** or **4b** were not successful. The difficulty in generating other 2-metalated thiazole species of the general structure **4** (where M = Cu, B, Ce) prompted us to search for other imino derivatives in which the electrophilic aptitude of the C=N group was enhanced.

Coupling of 2-Metalated Thiazoles 4a and 4b to α-Amido Sulfone 19. On the basis of our protecting group choice for the GE2270 A eastern fragment **3**, it can be concluded that the most expeditious synthetic route would involve the use of an *N*-acylimine. Addition of a 2-thiazolylmetal species to a *N*-*tert*-butyloxycarbonylimino derivative would lead directly to the amino alcohol with the desired set of protecting groups in place. However, these imino derivatives are too unstable to be stored, and must be generated in situ from a suitable precursor. α-Amido sulfones are convenient solid compounds that in the presence of a base of sufficient strength undergo elimination to yield the corresponding *N*-acyl imines.[47]

The required α-amido sulfone **19** was obtained after treatment of aldehyde (*S*)-**16** with benzenesulfinic acid and *tert*-butyl carbamate in dichloromethane, following the anhydrous protocol developed by Petrini and co-workers.[48] Compound **19**, isolated as a mixture of diastereoisomers, was directly submitted to the elimination−addition reaction with 2 equiv of the 2-thiazolyl reagents **4a** and **4b**. Regardless of the nature of the metal

SCHEME 6



employed, the undesired *threo*-protected amino alcohol **7** was preferentially formed. The low yield (23−27% over 2 steps) and the sense of diastereoselection precluded any further optimization of this reaction sequence.

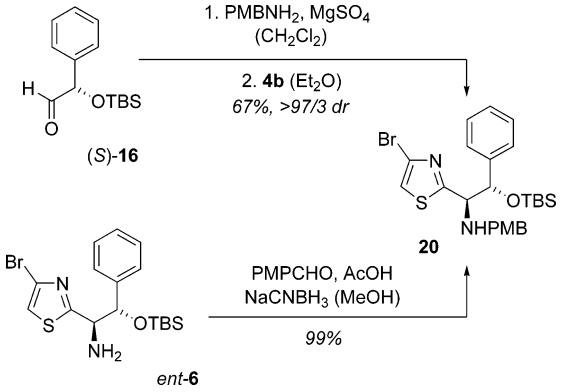
2-Thiazolyl Additions to *N*-*p*-Methoxybenzyl (PMB) Imines. Our search for synthetically useful enantiomerically pure aldimines derived from mandelic aldehyde drew our attention to the work by Poisson and Normant on the addition of configurationally stable allenyl zinc reagents to enantiomerically enriched benzylimines.[49,50] They described the use of *O*-TBS protected mandelic aldehyde (**16**) as a configurationally stable imine precursor, simply by the addition of benzylamine and $MgSO_4$ in toluene at 0 °C.[51−53] Interestingly, the only product observed in the allenylzinc addition was shown to be *erythro* configurated, the desired stereochemistry for our amino alcohol system.

It was envisioned that the application of this strategy to the nucleophilic addition of 4-bromo-2-lithiothiazole (**4b**) might be feasible, leading to an identical stereochemical outcome. However, due to the anticipated incompatibility between the 4-bromothiazole moiety and the hydrogenolysis conditions,[54] generally employed to deprotect *N*-benzyl amino groups, our attention turned to the preparation of the analogous *p*-methoxybenzyl aldimine. While the latter compounds should display similar reactivity, the cleavage of the incorporated PMB protecting group should be possible under oxidative conditions. Hence, treatment of the freshly prepared aldehyde (*S*)-**16** with 1 equiv of *p*-methoxybenzylamine in CH_2Cl_2 at room temperature, in the presence of a drying agent ($MgSO_4$), yielded the desired imine. This intermediate was found to be unstable to exposure to silica gel, being directly used in the next step after filtration of the magnesium salt and elimination of the solvent. We were pleased to find that upon addition of the lithiated thiazole **4b** at −78 °C in Et_2O, only one diastereoisomer was formed in good yield (Scheme 7).

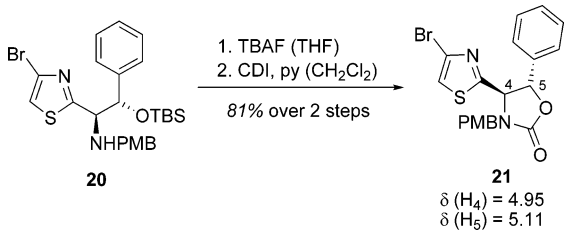
To determine the stereochemical outcome of the 2-thiazole addition, the cyclic oxazolidinone derivative **21** was prepared in two steps (Scheme 8, CDI = 1,1′-carbonyldiimidazole). Unfortunately, we were unable to unambiguously establish the configuration of the generated stereocenter by spectroscopic means. While the *J*-based configurational analysis proved inconclusive in establishing the spatial relationship between the phenyl and thiazolyl substituents ($^3J_{H4-H5}$ = 6.3 Hz),[55] the 2D-NOESY did not exclusively display the contacts expected for either a *trans* or *cis* configuration. We could finally determine the stereochemical configuration via chemical synthesis. Protec-

(43) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahamas, S.; Yamazaki, N. *Synthesis* **1982**, 461−462.
(44) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289−294.
(45) Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745−8747.
(46) Akiba, T.; Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Terashima, S. *Tetrahedron* **1994**, *50*, 3905−3914.
(47) Review: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949−3977.
(48) Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2002**, *67*, 2989−2994.
(49) Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560.
(50) Poisson, J. F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889−1891.
(51) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853−1868.
(52) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158−1161.
(53) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746−4748.
(54) Kerdesky, F. A. J.; Seif, L. S. *Synth. Commun.* **1995**, *25*, 4081−4086.

SCHEME 7



SCHEME 8

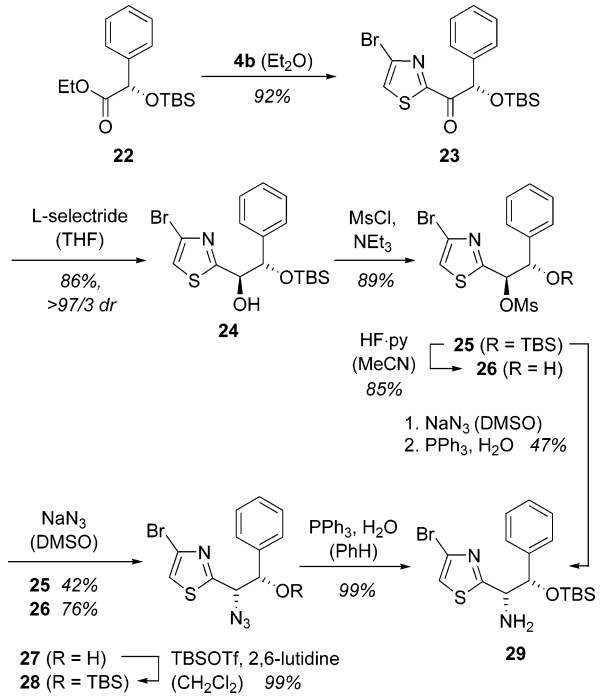


tion of the *threo* configured *ent*-**6**, which was obtained utilizing the addition−reduction sequence described above, as the *p*-methoxybenzyl derivative yielded a synthetic material with identical spectroscopic properties to **20**.

This experiment represents another example in which the presence of the 2-thiazolyl substituent leads to an unexpected stereochemical outcome in the 1,2-induction process. The observed sense of induction could not be overturned by varying the solvent or the nature of the organometallic species. While the *threo* isomer was the only product isolated when toluene was used as solvent, no reaction took place in THF. This was also the case when the coupling of thiazolylmagnesium **4a** to the (*S*)-configurated mandelic imine was attempted, presumably due to the insufficient nucleophilicity of the Grignard reagent.

Synthesis of *Erythro* Amino Alcohol via S_N2 Inversion with Sodium Azide. Due to the problems found in the stereoselective construction of the amino alcohol moiety employing unsaturated nitrogen compounds, our attention turned to the use of carbonyl derivatives as electrophiles in the 2-thiazolyl addition reaction. This strategy would benefit from the higher stability and electrophilicity of the latter compounds, relative to their analogous imines. Importantly, there was precedence in the nucleophilic addition to *O*-TBS protected mandelic acid derivatives,[56−59] facilitating the prediction of the stereochemical outcome of our envisaged reaction. The introduction of the amino group would then be carried out in a subsequent nucleophilic substitution process, after activation of the corresponding alcohol.

SCHEME 9



We started our synthesis from the protected (*S*)-mandelate **22**, which was prepared according to the literature procedure.[40] Reaction with the 2-lithio thiazole derivative **4b** (1.15 equiv) in Et_2O provided the single addition product **23** in excellent yield. Since we planned to introduce the amino moiety with a stereochemical inversion at the carbon atom α to the 2-thiazolyl moiety, we required a method that would reduce ketone **23** under Felkin−Anh control. In the event, reduction of ketone **23** with L-selectride in THF at −78 °C provided exclusively the required *threo* alcohol **24**, which was subsequently mesylated in 89% yield. The *O*-TBS protected azide **28** could be prepared directly, although in modest yield (42%), by addition of NaN_3 to a solution of mesylate **25** in DMSO.[60] This reaction proceeded with complete inversion, and none of the undesired *threo* azide could be detected. The choice of azide **28** as forerunner of our desired free amine initially turned out to be problematic, due to the quick debromination at the thiazole heterocycle under standard catalytic hydrogenation conditions (1 bar H_2, Pd/C, or $Pd(OH)_2$). However, the Staudinger reduction of the azide proceeded smoothly to yield the desired *erythro* amino alcohol **29** in quantitative yield. Interestingly, DMSO proved to be a suitable solvent for the Staudinger reaction. This observation was exploited in a more practical synthesis of amine **29**, which involved the stepwise addition of sodium azide, triphenylphosphine, and water to a DMSO solution of mesylate **25** at 90 °C. The low yield observed in the mesylate displacement reactions was attributed to the partial decomposition of the nascent azide under the forcing reaction conditions. To reduce the steric congestion around the mesylate stereocenter, we carried out the azidation reaction on the free alcohol **26**, which could be

(55) In five-membered heterocyclic ring systems it is generally accepted that the trans coupling constant is smaller than 4.0 Hz: (a) Nadir, U. K.; Basu, N. *Tetrahedron* **1993**, *49*, 7787−7792. However, there are reports describing trans compounds similar to **21**, for which coupling constants of 7 Hz have been measured: (b) Sugiyama, S.; Morishita, K.; Chiba, M.; Ishii, K. *Heterocycles* **2002**, *57*, 637−648. (c) Dinsmore, C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885−2888.

(56) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, *5*, 831−834.

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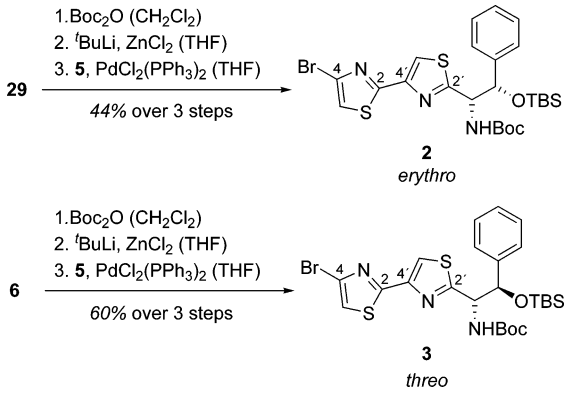
(58) Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 523−527.

(59) Surivet, J. P.; Gore, J.; Vatele, J. M. *Tetrahedron Lett.* **1996**, *37*, 371−374.

(60) For a recent review on the chemistry of azides, see: Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

SCHEME 10



obtained in 85% yield after desilylation of **25**. With the new substrate the azide introduction could be carried out at a lower temperature (65 °C instead of 90 °C), leading to a considerable improvement in the chemical yield (from 42% to 76%). The following TBS protection of alcohol **27** proceeded uneventfully to yield **28** in excellent yield. Depending on the amination strategy employed, the (*S*,*S*)-amino alcohol **29** could be obtained in 5−8 steps and 33−44% overall yield, starting from commercially available ethyl (*S*)-mandelate.

Thiazole Homologation at C4 via Cross-Coupling. Once we had access to the amino alcohol fragment in either diastereomeric form, we planned to build the 2,4′-bithiazole applying our regioselective Pd-mediated cross-coupling methodology. Prior to this, protection of the amino group as the *N*-*tert*-butyloxycarbonyl derivative was carried out under standard conditions (Scheme 10).

Preparation of the 4-thiazolylzinc reagent required for the following Negishi coupling step was achieved by low-temperature lithium−bromine exchange and subsequent transmetalation to zinc. Crucial in this process was the slow addition of *t*-BuLi to a THF solution of $ZnCl_2$ and the corresponding 4-bromothiazole. Previous studies in our group had shown that the lithium−bromine exchange of 4-bromothiazoles containing the NHBoc moiety leads to 5-lithiated thiazoles, presumably after mediation of the amide proton.[61,62] Addition of 2,4-bromothiazole (**5**) and the corresponding palladium catalyst yielded the desired 2,4′-bithiazoles, in both stereochemical configurations, in moderate to good yield. A second *umpolung* operation at the 4-position in bithiazole **2** should give the corresponding organometallic species (M = Zn or Sn), ready to participate in the final Pd-mediated coupling to the pyridine core of the GE2270 antibiotics.

Conclusions

In summary, we have reported an efficient synthesis of the eastern subunit of the GE2270 antibiotics employing 2,4-dibromothiazole as the key building block. The construction of the amino alcohol can be carried out by direct coupling of a 4-bromo-2-thiazolyl nucleophile to C−N unsaturated electrophiles, leading preferentially to the formation of *threo* isomers. To obtain the (*S*,*S*)-*erythro* diastereoisomer, a strategy involving the quenching of 2-lithio derivative **4b** with TBS protected ethyl (*S*)-mandelate and subsequent diastereoselective reduction was developed. The free amine could be introduced in two synthetic operations from alcohol **24** simply by mesylation and a one-pot nucleophilic azidation−reduction sequence. A Negishi cross-coupling reaction was employed to regioselectively assemble the 2,4′-bithiazoles **2** and **3**, ready to undergo further elaboration at the bromine position. According to our GE2270 A synthetic strategy, the herein described *erythro* stereoisomer **2** is envisioned to react with a fully functionalized 2-bromopyridine in the final key C−C bond forming reaction. Our progress in this field will be reported in due course.

Experimental Section

All reactions were carried out following our reported general experimental protocol.[63] $PdCl_2(PPh_3)_2$,[64] 2,4-dibromothiazole (**5**),[33] (*tert*-butyldimethylsilyloxy)benzeneacetonitrile,[65,66] 2-(*tert*-butyldimethylsilyloxy)-2-phenylacetaldehyde (**16**),[40,67] and ethyl (*tert*-butyldimethylsilyloxy)mandelate (**22**)[67] were prepared according to literature procedures.

(−)-(1*S*,2*R*)-1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine (6) and (+)-(1*R*,2*R*)-1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine (*ent*-29). To a stirred solution of 2,4-dibromothiazole (**5**) (2.92 g, 12.0 mmol) in THF (30 mL) at 0 °C was added *i*-PrMgBr (6.60 mL, 12.0 mmol, 1.80 M in ether). After 30 min, *O*-TBS protected mandelonitrile (2.47 g, 10.0 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then for 30 min at room temperature. Ethanol (10 mL) was added and upon cooling to −78 °C $NaBH_4$ (0.76 g, 20.0 mmol) was added in small portions. The reaction mixture was stirred for 2 h at −78 °C and then allowed to reach room temperature overnight. After the careful addition of saturated aq NH_4Cl solution (200 mL) ether (200 mL) was added. The organic layer was washed with H_2O (200 mL) and brine (100 mL) and dried (Na_2SO_4). GC analysis indicated a facial diastereoselectivity of 79:21. The solvent was removed and the residue was purified by flash chromatography (P/Et_2O = 75:25 → 50:50) to yield amine **6** (2.55 g, 6.18 mmol, 62%) as a pale yellow oil and its epimer *ent*-**29** as a pale yellow oil (0.47 g, 1.13 mmol, 11%). Major *threo* adduct **6**: R_f 0.30 (P/Et_2O = 75:25); $[\alpha]^{20}_D$ −47.8 (*c* 1.50 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.26 (s, 3 H), −0.22 (s, 3 H), 0.76 (s, 9 H), 1.80 (s, 2 H), 4.10 (d, ^3J = 1.9 Hz, 1 H), 5.49 (d, ^3J = 1.9 Hz, 1 H), 7.13 (s, 1 H), 7.26−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.7, −4.8, 18.0, 25.7, 60.8, 76.7, 117.2, 124.4, 126.1, 127.6, 128.2, 141.8, 177.6. Anal. Calcd for $C_{17}H_{25}BrN_2OSSi$ (413.45): C, 49.39; H, 6.09; N, 6.78. Found: C, 49.47; H, 5.88; N, 6.73. Minor *erythro* adduct *ent*-**29**: R_f 0.11 (P/Et_2O = 75:25); $[\alpha]^{20}_D$ +20.4 (*c* 1.05 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.21 (s, 3 H), 0.06 (s, 3 H), 0.82 (s, 9 H), 2.02 (br s, 2 H), 4.41 (d, ^3J = 5.9 Hz, 1 H), 5.04 (d, ^3J = 5.9 Hz, 1 H), 7.09 (s, 1 H), 7.19−7.26 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.3, −4.8, 18.0, 25.7, 60.6, 78.2, 117.0, 124.3, 127.0, 128.0, 128.1, 140.1, 173.9. Anal. Calcd for $C_{17}H_{25}BrN_2OSSi$ (413.45): C, 49.39; H, 6.09; N, 6.78. Found: C, 49.54; H, 6.11; N, 6.71.

(±)-(1*S,2*R**)-[1-(4-Bromothiazol-2-yl)-2-hydroxy-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (*rac*-8).** A solution of *rac*-**7** (257 mg, 500 μmol) in THF (5 mL) was cooled to 0 °C and TBAF (1.00 mL, 1.00 mmol, 1 M in THF) was added dropwise. After being stirred for 1 h at 0 °C the reaction mixture was diluted with ether (30 mL) and washed with H_2O (3 × 30 mL) and brine (30

(61) Heckmann, G. Ph.D. Thesis, Technische Universität München, 2004.
(62) For a similar observation, see: Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381−2385.
(63) Lemarchand, A.; Bach, T. *Synthesis* **2005**, 1977−1990.
(64) Hartley, F. R. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 119−137.
(65) Brussee, J.; Roos, E. C.; van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485−4488.
(66) Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809−3826.
(67) Hayashi, M.; Yoshiga, T.; Nakatani, K.; Ono, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 2821−2830.

mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo and the crude product was purified by flash chromatography (P/Et_2O = 60:40) to yield *rac*-**8** (181 mg, 453 μmol, 91%) as a pale yellow oil. R_f 0.46 (P/Et_2O = 50:50); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.25 (s, 9 H), 3.32 (d, ^3J = 3.0 Hz, 1 H), 5.17 (dd, ^3J = 2.5 Hz, ^3J = 9.2 Hz, 1 H), 5.49 (br s, 1 H), 5.59 (d, ^3J = 9.2 Hz, 1 H), 7.17 (s, 1 H), 7.26−7.38 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 28.1, 57.9, 74.2, 80.4, 117.5, 124.5, 126.0, 127.9, 128.4, 139.4, 155.4, 172.5. Anal. Calcd for $C_{16}H_{19}BrN_2O_3S$ (399.30): C, 48.13; H, 4.80; N, 7.02. Found: C, 48.02; H, 4.99; N, 6.68.

(±)-(4*S,5*R**)-4-(4-Bromothiazol-2-yl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (*rac*-9).** A solution of *rac*-**8** (149 mg, 373 μmol), *p*-TSA (7.6 mg, 10 mol %), and 2,2-dimethoxypropane (1.11 mL) in 2.5 mL of CH_2Cl_2 was stirred at room temperature for 24 h. After that the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aq $NaHCO_3$ solution (5 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product purified by flash chromatography (P/Et_2O = 75:25) to give *rac*-**9** (134 mg, 305 μmol, 82%) as colorless crystals. Mp 129−130 °C; R_f 0.49 (P/Et_2O = 75:25); ^{1}H NMR (DMSO-d_6, T = 60 °C, 360 MHz) δ 1.24 (s, 9 H), 1.70 (s, 3 H), 1.72 (s, 3 H), 4.95 (d, ^3J = 7.8 Hz, 1 H), 5.11 (d, ^3J = 7.8 Hz, 1 H), 7.32−7.38 (m, 5 H), 7.77 (s, 1 H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 25.6, 26.2, 27.8, 65.6, 80.1, 82.8, 95.0, 118.6, 123.2, 127.2, 128.6, 129.0, 136.5, 150.7, 171.3. Anal. Calcd for $C_{19}H_{23}BrN_2O_3S$ (439.37): C, 51.94; H, 5.28; N, 6.38. Found: C, 51.67; H, 5.25; N, 6.31.

(±)-2-[(1*S,2*R**)-*tert*-Butoxycarbonylamino-(*tert*-butyldimethylsilyloxy)-2-phenylethyl]thiazole-4-carboxylic Acid Ethyl Ester (*rac*-13).** A solution of *t*-BuLi (1.15 mL, 1.95 mmol, 1.5 M in pentane) in ether (1 mL) was cooled to −78 °C and the solution of *rac*-**7** (250 mg, 489 μmol) in ether (2 mL) was added dropwise. After 10 min of stirring at −78 °C powdered CO_2 (3 g) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue dissolved in DMF (6 mL). After the addition of K_2CO_3 (668 mg, 4.89 mmol) and EtI (0.41 mL, 766 mg, 4.89 mmol) the solution was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (3 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by flash chromatography (P/Et_2O = 75:25) to yield the 4-ethoxycarbonylthiazole *rac*-**13** (116 mg, 229 μmol, 47%) as a colorless oil. R_f 0.45 (P/Et_2O = 50:50); ^{1}H NMR (DMSO-d_6, 360 MHz) δ −0.31 (s, 3 H), −0.29 (s, 3 H), 0.71 (s, 9 H), 1.27−1.31 (m, 12 H), 4.26−4.33 (m, 2 H), 5.00 (dd, ^3J = 3.2 Hz, ^3J = 9.1 Hz, 1 H), 5.36 (d, 1 H, ^3J = 3.2 Hz), 7.23−7.43 (m, 6 H), 8.41 (s, 1 H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ −5.5, −4.9, 14.4, 17.9, 25.7, 28.2, 59.9, 60.8, 76.0, 79.0, 126.7, 127.6, 128.0, 129.2, 141.1, 146.2, 155.4, 160.9, 173.2. Anal. Calcd for $C_{25}H_{38}N_2O_5SSi$ (506.73): C, 59.26; H, 7.56; N, 5.53. Found: C, 59.59; H, 7.34; N, 5.46.

(±)-(4*R,5*S**)-4-(4-Ethoxycarbonylthiazol-2-yl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (*rac*-14).**[13a] A solution of *rac*-**13** (87.0 mg, 172 μmol) in THF (5 mL) was cooled to 0 °C and TBAF (0.34 mL, 340 μmol, 1 M in THF) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 2 h at room temperature. After dilution with EtOAc (20 mL) it was washed with H_2O (2 × 20 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and *p*-TSA (6.5 mg, 10 mol %) and 2,2-dimethoxypropane (0.5 mL) were added, and the solution was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with $NaHCO_3$ solution (20 mL, 5% in H_2O), and dried (Na_2SO_4). After the solvent was removed the crude product was purified by flash chromatography (P/Et_2O = 80:20 → 70:30) to yield *rac*-**14** (53.7 mg, 124 μmol, 72%) as colorless crystals. The analytical data are in accordance with the literature.[13a] Mp 129−130 °C; R_f 0.48 (P/Et_2O = 50:50); ^{1}H NMR (DMSO-d_6, T = 60 °C, 360 MHz) δ 1.21 (s, 9 H), 1.28 (t, ^3J = 7.0 Hz, 3 H), 1.71 (s, 3 H), 1.74 (s, 3 H), 4.28 (t, ^3J = 7.0 Hz, 2 H), 4.99 (d, ^3J = 7.7 Hz, 1 H), 5.16 (d, ^3J = 7.7 Hz, 1 H), 7.36 (br s, 5 H), 8.48 (s, 1 H); ^{13}C NMR (DMSO-d_6, T = 60 °C, 90 MHz) δ 14.0, 25.7, 27.6, 60.6, 65.4, 94.9, 126.8, 128.4, 128.6, 128.9, 136.6, 145.7, 160.4, 170.7.

(±)-(1*S,2*R**)-2-(*tert*-Butyldimethylsilyloxy)-1,2-diphenylethylamine (*rac*-17).**[37b] A solution of hexamethyldisilazane (91.0 μL, 70.9 mg, 440 μmol) in THF (3 mL) was cooled to −78 °C, and *n*-BuLi (160 μL, 400 μmol, 2.5 M in pentane) was added dropwise. The mixture was warmed to room temperature, stirred for 10 min, and again cooled to −78 °C. A solution of aldehyde *rac*-**16** (100 mg, 400 μmol) in THF (2 mL) was added, followed after 15 min by PhLi (278 μL, 500 μmol, 1.8 M in hexanes). After an additional 15 min of stirring at −78 °C the reaction mixture was slowly warmed to room tempearture, quenched with saturated aq NH_4Cl solution (20 mL), and extracted with ether (30 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (P/EtOAc = 75:25) to yield 60.0 mg (183 μmol, 46%) of *rac*-**17** as a yellow oil in diastereomerically pure form. The analytical data were in accordance with the literature.[37b] R_f 0.25 (P/ EtOAc = 75:25); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.23 (s, 3 H), −0.13 (s, 3 H), 0.85 (s, 9 H), 1.74 (br s, 1 H), 3.98 (d, ^3J = 5.5 Hz, 1 H), 4.65 (d, ^3J = 5.5 Hz, 1 H), 7.11−7.22 (m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.5, −4.8, 18.2, 25.9, 63.2, 80.5, 126.7, 126.9, 127.1, 127.5, 127.7, 127.8, 142.5, 142.6.

(±)-(4*R,5*R**)-Diphenyloxazolidin-2-one (*rac*-18).**[45] A solution of *rac*-**17** (48.6 mg, 148 μmol) in acetonitrile (1 mL) and HF (1 mL, 50% in H_2O) was stirred for 16 h at 50 °C. After the solution was cooled to room temperature the pH value was adjusted to 12 with NaOH solution (5% in H_2O). H_2O (50 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with methanol (3 mL) and HCl (0.5 mL, 36% in H_2O) and again concentrated in vacuo. The remaining solid and triethylamine (63.0 μL, 46.0 mg, 450 μmol) were dissolved in CH_2Cl_2 (2.0 mL) and cooled to 0 °C. Diphosgene (11.0 μL, 17.8 mg, 90.0 μmol) was added and the mixture was stirred for 1 h at 0 °C. The solvents were removed in vacuo, and the residue was suspended in H_2O (5 mL) and stirred at room temperature overnight. The solid was filtered, washed with HCl solution (10% in H_2O) and H_2O, and dried in vacuo to yield *rac*-**18** (18.2 mg, 76.1 μmol, 51%) as pale yellow crystals. The analytical data were in accordance with the literature.[45] ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.74 (d, ^3J = 7.3 Hz, 1H), 5.28 (d, ^3J = 7.3 Hz, 1 H), 5.75 (s, 1 H), 7.21−7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 64.9, 86.1, 125.0, 125.6, 128.0, 128.2, 128.2, 128.4, 137.3, 138.4, 158.6.

(+)-(1*R*,2*S*)-[1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethyl]-(4-methoxybenzyl)amine (20). Method A: To a stirred solution of aldehyde (*S*)-**16** (200 mg, 0.798 mmol) in CH_2Cl_2 (2 mL) were added *p*-methoxybenzylamine (125 μL, 0.958 mmol) and $MgSO_4$ (483 mg, 4.00 mmol) at room temperature and the stirring was continued for 2 h. Filtration of the magnesium salts and removal of the solvent in vacuo gave the corresponding imine, which was subsequently used without further purification. To a stirred solution of *n*-BuLi (319 μL, 0.798 mmol, 2.5 M in hexane) in Et_2O (2 mL) at −78 °C was added a solution of 2,4-dibromothiazole (**5**) (193 mg, 0.798 mL) in Et_2O (3 mL) and the mixture was stirred for 1 h. A solution of freshly prepared imine, prepared as described above, in Et_2O (2 mL) was added to the reaction mixture via cannula. After 2 h at −78 °C, the reaction mixture was allowed to warm to 0 °C and saturated aq NH_4Cl solution (10 mL) was carefully added. The mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/Et_2O = 95:5) yielded amine **20** (285 mg, 0.534 mmol, 67%) as a pale yellow oil. **Method B:** To a stirred solution of amine *ent*-**6** (220 mg, 0.53 mmol), *p*-anisaldehyde (71 μL, 79

mg, 0.53 mmol), and $NaCNBH_3$ (30 mg, 0.48 mmol) in MeOH (1 mL) at 0 °C was added acetic acid (20 μL). The reaction mixture was allowed to warm to room temperature overnight and then partitioned between saturated aq NH_4Cl solution (10 mL) and Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/Et_2O = 95:5) yielded amine **20** (280 mg, 0.525 mmol, 99%) as a pale yellow oil. R_f 0.57 (P/Et_2O = 4:1); $[\alpha]^{20}_D$ +28.7 (*c* 1.00 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.26 (s, 3 H), −0.22 (s, 3 H), 0.79 (s, 9 H), 2.60 (br s, 1 H), 3.28−3.37 (m, 1 H), 3.77 (s, 3 H), 4.02 (d, ^3J = 2.8 Hz, 1 H), 5.36 (d, ^3J = 2.8 Hz, 1 H), 6.73−6.76 (m, 2 H), 6.93−6.96 (m, 2 H), 7.14 (s, 1 H), 7.30−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.7, −4.9, 18.1, 25.7, 52.2, 55.2, 65.7, 76.9, 113.6, 117.6, 124.2, 126.0, 127.6, 128.3, 129.3, 131.7, 141.7, 158.6, 178.1; HRMS (EI) calcd for $C_{21}H_{23}N_2O_2SSiBr$ [(M − C_4H_9)$^+$] 477.0490, found 477.0512.

(−)-(2*S*)-1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethanone (23). To a stirred solution of *n*-BuLi (3.40 mL, 8.5 mmol, 2.5 M in hexane) in Et_2O (30 mL) at −78 °C was added a solution of 2,4-dibromothiazole (**5**) (2.06 g, 8.5 mmol) in Et_2O (15 mL) over 1 h. After 1 h at −78 °C, a precooled solution of methyl ester **22** (2.16 g, 7.72 mmol) in Et_2O (10 mL) was added via cannula. The reaction mixture was allowed to warm to 0 °C, before it was partitioned between saturated aq NH_4Cl solution (50 mL) and Et_2O (3 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/Et_2O = 95:5) yielded ketone **23** (2.92 g, 7.10 mmol, 92%) as a colorless oil. R_f 0.46 (P/Et_2O = 80:20); $[\alpha]^{20}_D$ −34.9 (*c* 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.03 (s, 3 H), 0.11 (s, 3 H), 0.92 (s, 9 H), 6.36 (s, 1 H), 7.27−7.34 (m, 3 H), 7.51−7.60 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −4.8 (2C), 18.3, 25.7, 76.5, 125.0, 127.2, 127.7, 128.3, 128.5, 137.7, 164.4, 189.2; HRMS (EI) calcd for $C_{13}H_{13}NO_2SiBr$ [(M − C_4H_9)$^+$] 353.9620, found 353.9612.

(+)-(1*R*,2*S*)-1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethanol (24). To a stirred solution of ketone **23** (1.06 g, 2.58 mmol) in THF (25 mL) at −78 °C was added L-selectride (4.14 mL, 4.14 mmol, 1 M in THF). After 1 h at −78 °C, the reaction mixture was quenched by the careful addition of saturated aq NH_4Cl solution (30 mL). The biphasic mixture was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/Et_2O = 95:5) yielded alcohol **24** (0.95 g, 2.30 mmol, 92%) as a white solid. Mp 67−69 °C; R_f 0.34 (P/Et_2O = 80:20); $[\alpha]^{20}_D$ +36.8 (*c* 0.83 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.23 (s, 3 H), −0.18 (s, 3 H), 0.80 (s, 9 H), 3.42 (d, ^3J = 8.6 Hz, 1 H), 4.90 (dd, ^3J = 8.6 Hz, ^3J = 1.8 Hz, 1 H), 5.34 (d, ^3J = 1.8 Hz, 1 H), 7.20 (s, 1 H), 7.30−7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.7, −4.9, 18.0, 25.7, 76.5, 76.6, 117.0, 124.6, 126.2, 127.9, 128.3, 140.5, 175.2; HRMS (EI) calcd for $C_{13}H_{15}NO_2SSiBr$ [(M − C_4H_9)$^+$] 355.9777, found 355.9776. Anal. Calcd for $C_{17}H_{24}BrNO_2SSi$ (414.43): C, 49.27; H, 5.84; N, 3.38. Found: C, 49.32; H, 5.76; N, 3.38.

(+)-(1*R*,2*S*)-Methanesulfonic Acid 1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethyl Ester (25). To a stirred solution of alcohol **24** (648 mg, 1.56 mmol) and triethylamine (440 μL, 3.17 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added mesyl chloride (120 μL, 2.38 mmol). After 1 h at −78 °C, the reaction mixture was quenched by the careful addition of saturated aq NH_4Cl solution (30 mL). The biphasic mixture was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/Et_2O = 95:5) yielded mesylate **25** (683 mg, 1.39 mmol, 89%) as a white solid. Mp 65−67 °C; R_f 0.26 (P/Et_2O = 4:1); $[\alpha]^{20}_D$ +49.7 (*c* 1.15 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.20 (s, 3 H), −0.19 (s, 3 H), 0.79 (s, 9 H), 2.39 (s, 3 H), 5.35 (d, ^3J = 3.4 Hz, 1 H), 5.76 (d, ^3J = 3.4 Hz, 1 H), 7.24 (s, 1 H), 7.28−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.5, −4.9, 18.2, 25.7, 37.8, 76.3, 84.2, 118.2, 125.2, 127.1, 128.6 (2C), 139.5, 167.9; HRMS (EI) calcd for $C_{14}H_{17}NO_4S_2SiBr$ [(M − C_4H_9)$^+$] 433.9552, found 433.9549.

(+)-(1*S*,2*S*)-2-Azido-2-(4-bromothiazol-2-yl)-1-phenylethanol (27). To a stirred solution of mesylate **26** (149 mg, 0.396 mmol) in DMSO (4 mL) was added sodium azide (39 mg, 0.594 mmol). The resulting solution was heated to 65 °C and the stirring continued for 2 h. After cooling to room temperature, the reaction was quenched by the slow addition of H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (P/EtOAc = 75:25). Azide **27** (99 mg, 282 μmol, 76%) was isolated as a yellow oil. R_f 0.27 (P/EtOAc = 80:20); $[\alpha]^{20}_D$ +12.3 (*c* 1.13 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.87 (d, ^3J = 2.6 Hz, 1 H), 4.92 (d, ^3J = 6.8 Hz, 1 H), 5.08 (dd, ^3J = 6.8, 2.5 Hz, 1 H), 7.24 (s, 1 H), 7.34−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 67.2, 76.9, 118.5, 125.2, 127.1, 128.8, 129.0, 138.6, 168.7. No satisfactory HRMS or elemental analysis data were obtained for this compound due to its instability.

(+)-(1*S*,2*S*)-2-[1-Azido-2-(*tert*-butyldimethylsilyloxy)-2-phenylethyl]-4-bromothiazole (28). Method A: To a stirred solution of mesylate **25** (197 mg, 0.40 mmol) in DMSO (4 mL) was added sodium azide (65 mg, 1.0 mmol). The resulting solution was heated to 90 °C and stirring was continued for 14 h. After cooling to room temperature, the reaction was quenched by the slow addition of H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (P/Et_2O = 85:15). Azide **28** (74 mg, 168 μmol, 42%) was isolated as a yellow oil. **Method B:** To a stirred solution of alcohol **27** (37.0 mg, 114 μmol) in CH_2Cl_2 (2 mL) at 0 °C was added 2,6-lutidine (38 μL, 342 μmol), followed by TBSOTf (38 μL, 171 μmol). After 2 h the reaction mixture was partitioned between saturated aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (P/EtOAc = 90:10) gave the TBS ether **28** (47.1 mg, 114 μmol, 100%) as a yellow oil. R_f 0.43 (P/Et_20 = 80:20); $[\alpha]^{20}_D$ +28.2 (*c* 1.00 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ −0.13 (s, 3 H), −0.06 (s, 3 H), 0.89 (s, 9 H), 5.06 (d, ^3J = 4.8 Hz, 1 H), 5.24 (d, ^3J = 5.0 Hz, 1 H), 7.16 (s, 1 H), 7.17−7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.2, −4.8, 18.1, 25.6, 68.3, 77.9, 118.1, 124.8, 127.0, 128.0, 128.3, 138.9, 167.0; HRMS (EI) calcd for $C_{13}H_{14}N_4OSSiBr$ [(M − C_4H_9)$^+$] 382.9820, found 382.9811.

(−)-(1*S*,2*S*)-1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine (29). Method A: To a stirred solution of mesylate **25** (398 mg, 0.81 mmol) in DMSO (6 mL) was added sodium azide (125 mg, 1.93 mmol). The resulting solution was heated to 90 °C and the stirring was continued for 14 h. Triphenylphosphine (697 mg, 2.66 mmol) was then added portionwise. After 4 h H_2O (1 mL) was added dropwise and the stirring was continued for 6 h. The reaction mixture was partitioned between H_2O (10 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (P/Et_2O = 50:50) to yield amine **29** (156 mg, 0.38 mmol, 47%) as a yellow oil. **Method B:** To a stirred solution of azide **28** (62 mg, 0.14 mmol) in benzene (1 mL) at 65 °C was added triphenylphosphine (74 mg, 0.28 mmol). After 3 h H_2O (200 μL) was added and the stirring was continued for 16 h. After being cooled to room temperature the reaction mixture was concentrated in vacuo. Flash chromatography (P/EtOAc = 70:30) gave amine **29** (58 mg, 0.14 mmol, 99%) as a yellow oil. $[\alpha]^{20}_D$ −20.4 (*c* 1.30 in $CHCl_3$).

(−)-(1*S*,2*S*)-[(4-Bromo-[2,4′]bithiazolyl-2′-yl)-(*tert*-butyldimethylsilyloxy)-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (2). To a stirred solution of Boc-protected **29** (109 mg, 213 μmol) and $ZnCl_2$ (0.74 mL, 744 μmol, 1.0 M) in THF (1.5 mL) at −78 °C was slowly added *t*-BuLi (0.44 mL, 744 μmol, 1.7 M in pentane).

The reaction mixture was stirred for 20 min at −78 °C and then warmed to room temperature. After the addition of 2,4-Dibromothiazole (**5**) (86.7 mg, 356 μmol) and bis(triphenylphosphine)-palladium(II) chloride (7.5 mg, 5 mol %) the stirring was continued at room temperature for 16 h. The reaction mixture was quenched with saturated aq NH_4Cl solution (1 mL) and concentrated in vacuo. EtOAc (10 mL) was added, and the organic layer was washed with saturated aq NH_4Cl solution (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (P/Et_2O = 90:10) to yield **2** (30.7 mg, 51 μmol, 24%, 44% borsm) as a yellow oil and recoverd starting material **29** (50.2 mg, 121 μmol, 40%) as a yellow oil. R_f 0.49 (P/Et_2O 75:25); $[\alpha]^{20}_D$ −1.7 (*c* 0.53 in $CHCl_3$); ^{1}H NMR (DMSO-d_6, T = 60 °C, 360 MHz) δ −0.32 (s, 3 H), −0.22 (s, 3 H), 0.65 (s, 9 H), 1.23 (s, 9 H), 4.94 (br s, 1 H), 5.09 (br s, 1 H), 7.26−7.43 (m, 6 H), 7.82 (s, 1 H), 8.25 (s, 1 H); ^{13}C NMR (DMSO-d_6, T = 60 °C, 90 MHz) δ −5.5, −5.1, 17.5, 25.3, 27.9, 75.7, 78.5, 118.5, 118.8, 124.8, 127.0, 127.6, 127.8, 141.3, 146.3, 163.1, 171.3. Anal. Calcd for $C_{25}H_{34}BrN_3O_3S_2Si$ (596.66): C, 50.32; H, 5.74; N, 7.04. Found: C, 50.64; H, 5.55; N, 6.95.

Acknowledgment. This project was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. We are grateful to the Universität Bayern e.V. for a predoctoral scholarship (H.M.M.) and to the Alexander von Humboldt Foundation for a postdoctoral research fellowship (O.D.). The donation of chemicals by DSM Fine Chemicals (Linz) and Wacker-Chemie (München) is gratefully acknowledged.

Supporting Information Available: General experimental methods, experimental procedures for compounds **7**, **10**, *rac*-**11**, *rac*-**12**, **21**, **26**, and **3**, and IR and MS data and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060462G