From Aziridines to Oxazolines and Thiazolines: The Heterocyclic Route to Thiangazole

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Abstract: Since its isolation in 1991, the polyazole natural product thiangazole has become a popular target for total synthesis due to its challenging array of heterocyclic segments and its reported potent antiviral activity. The synthetic activity toward thiangazole is reviewed and a novel approach that takes advantage of aziridine and oxazoline intermediates en route to thiazolines is presented.

1. Introduction

The presence of multiple directly-linked five-membered heterocycles is an intriguing structural characteristic of tantazoles[1] and mirabazoles[2] as well as the macrocyclic ulapualides,[3] kabiramides,[4] halichondramides[5] and mycalolides[6] (Figures 1 and 2).[7] Several other natural products, among them bleomycin,[8] diazonamide,[9] hennoxazole,[10] microcin B17,[11] muscoride A,[12] and myxothiazol[13] contain bi-azoles, e.g. directly linked thiazole or oxazole units, as part of their backbone structure (Figure 3).

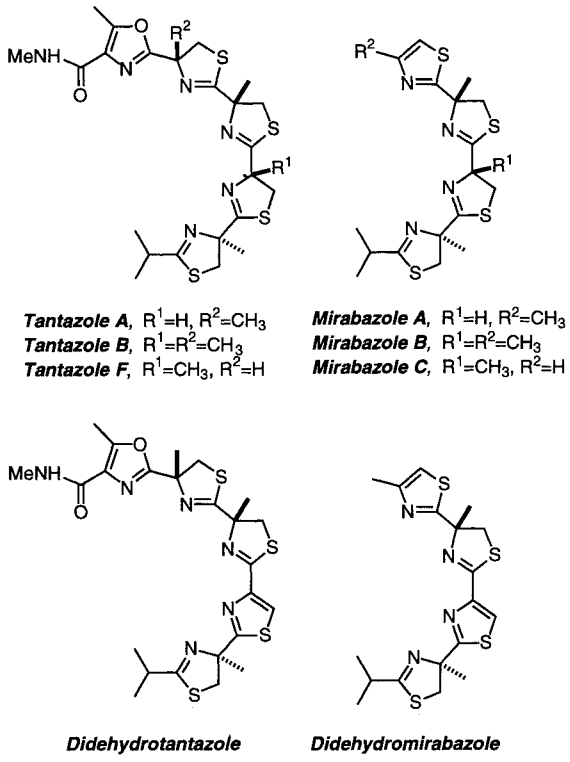


Figure 1. Polyazoles from the blue-green alga *Scytonema mirabile*.

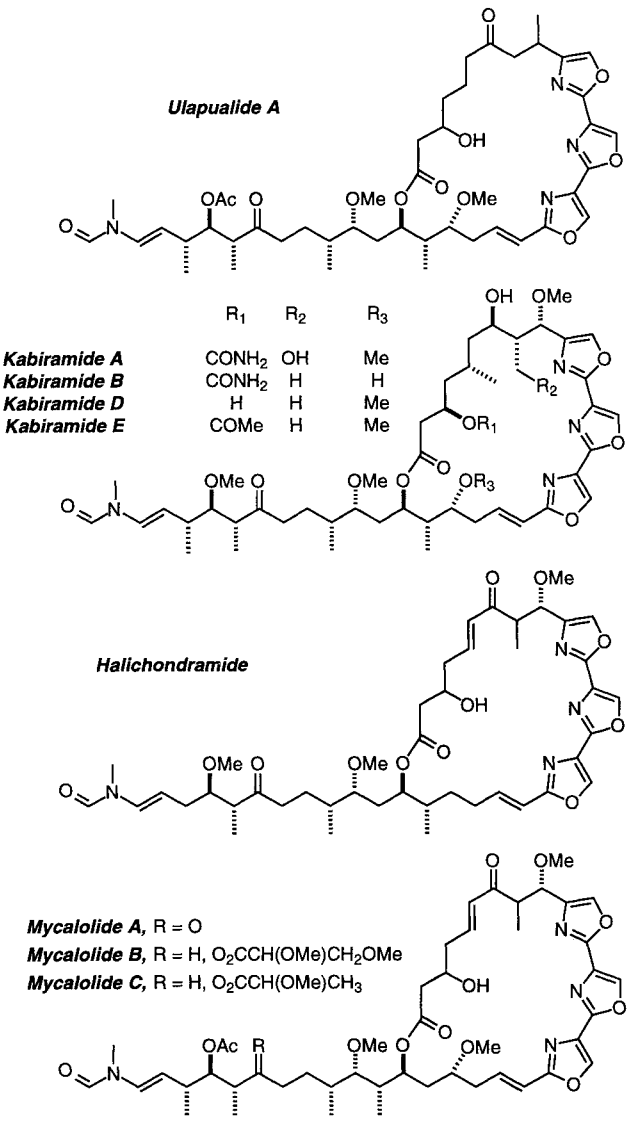


Figure 2. Polyazoles from the sponges *Halichondria* and *Mycale* and *Hexabranchus sanguineus* egg masses.[22]

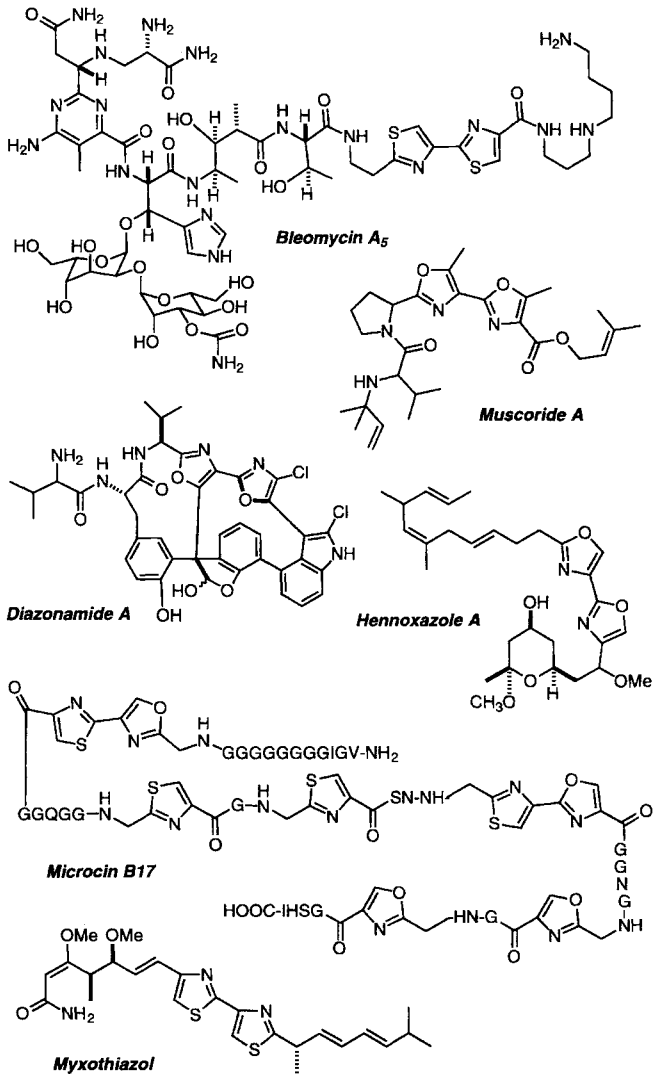


Figure 3. Bi-azole natural products.

Remarkable cytotoxic and antitumor properties were recorded for most members of the polyazole group of natural products. In 1992, another member of this class, thiangazole (**1**) was isolated from a myxobacterium *Polyangium sp.* strain (Figure 4).[14] Structurally a hybrid between tantazoles and mirabazoles, thiangazole attracted immediate interest due to its broad spectrum of biological activities. Reports of antihelmintic and antifungal effects,[15] and, especially, its extremely high potency in HIV-1 inhibition[14,16] have triggered several synthetic,[17,18,19] structural,[20] and biological[21] investigations. Thiangazole was initially reported to inhibit HIV-1 infection in MT-4 cell assays with an IC_{100} of 4.7 pM without noticeable toxicity at up to millimolar levels![14] The lack of cytotoxicity for this compound appeared especially surprising considering the moderate to high levels of cytotoxicity observed with the mirabazoles and tantazoles.

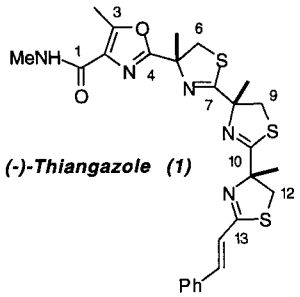
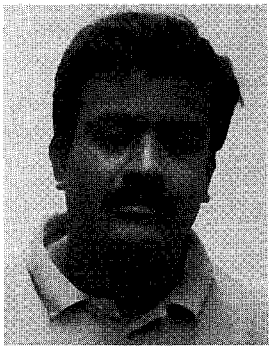


Figure 4. The *Polyangium sp.* metabolite thiangazole.

As an extension of our synthetic studies of marine natural products and alkaloids,[23] we chose to embark on a total synthesis of thiangazole to demonstrate and further expand the methodology we had developed previously for the preparation of five-membered heterocycles.[24] Concurrent with our work, the groups of Pattenden, Ehrler, and Heathcock were also actively pursuing the total synthesis of thiangazole.[25]

In Pattenden's approach,[17] the building block (*R*)-α-methylcysteine was prepared by an extension of Seebach's "self-regeneration of chirality" protocol (Scheme 1).[26] Alkylation of thiazolidine **4** with methyl iodide provided exclusively the *cis*-isomer **5** which was converted to the desired α-methyl amino acid ester **6** in an



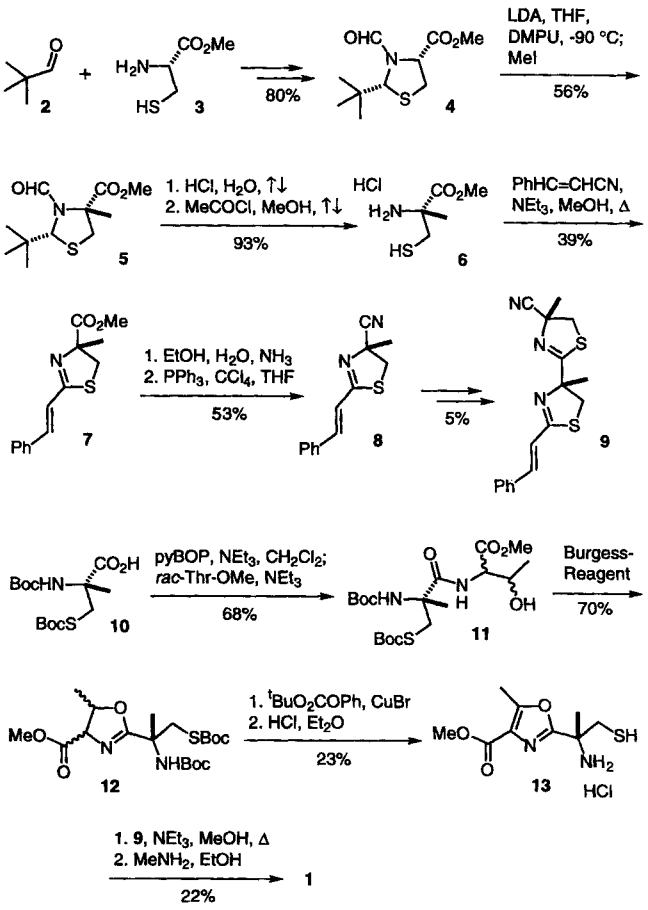
Peter Wipf received his Diploma in 1984 and his PhD in 1987 from the University of Zürich under the direction of Prof. Heinz Heimgartner. He continued his scientific eduction as a Swiss NSF Posidoctoral Fellow at the University of Virginia with Prof. Robert E. Ireland. In 1990, he joined the faculty at the University of Pittsburgh as an Assistant Professor, and was promoted to Associate Professor in 1995. His research interests focus on the total synthesis of biologically active natural products, structural studies of marine metabolites, the development of new protocols for the preparation of heterocycles and peptide mimetics, and the chemistry of organozirconocenes.

Peter Wipf has been named a Lilly Grantee and an NSF Presidential Faculty Fellow. He has also received a Camille Dreyfus Teacher-Scholar Award, an Alfred P. Sloan Foundation Fellowship, an American Cancer Society Junior Faculty Award, the ETH Ruzicka Award, an American Cyanamid Young Faculty Award, the Merck Young Investigator Award, and the Zeneca Award for Excellence in Chemistry.

Srikanth Venkatraman was born in Madras, India, in 1968 and received his BS in Chemistry in 1989 at Vivekananda College and his MS in 1991 from the Indian Institute of Technology in Madras. He joined the Wipf group in 1991 and has worked on the Sm→Cu transmetalation and natural products synthesis. He recently accomplished the total syntheses of thiangazole and muscoride A.

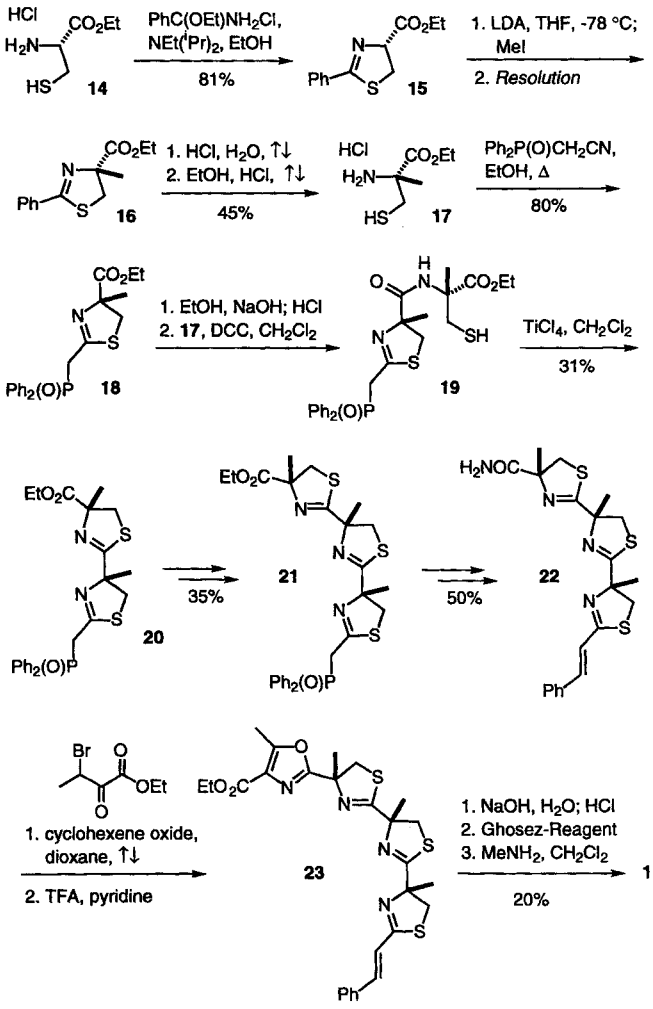
overall yield of 42% from L-cysteine **3**. The preparation of the thiazoline segments was accomplished by an iterative protocol involving the conversion of the methyl ester to the primary amide, dehydration to the nitrile, and cyclocondensation with amino thiol **6**. The oxazole moiety was obtained by acylation of racemic threonine with *bis*-Boc-protected α-methyl cysteine **10** in the presence of benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (pyBOP)[27] followed by cyclodehydration with Burgess reagent[24] and oxidation of oxazoline **13** with *t*-butylperoxybenzoate and copper(I) bromide.[28] After cleavage of the Boc protective groups, oxazole segment **13** was obtained in 16% yield from dipeptide **11**. The final segment condensation between nitrile **9** and amino thiol **13** provided (-)-thiangazole (**1**) in an overall yield of 0.1% calculated for the longest linear sequence.

In the total synthesis of thiangazole reported by Ehrler and Farooq,[18] (*R*)-α-methylcysteine **17** was prepared in 37% yield from L-cysteine by resolution of methylated thiazoline **16** by preparative HPLC on cellulose triacetate (Scheme 2). The iterative synthesis of the three thiazoline rings took advantage of Heathcock's $TiCl_4$ protocol[2d] for the cyclodehydration of cysteine amides and provided tricycle **22** in 4% yield from **17**. The terminal oxazole ring was formed by reaction of **22** with 3-bromooxobutyrate and dehydration of the resulting 4-hydroxyoxazoline with trifluoroacetic anhydride in pyridine. After ester saponification and conversion of the acid to the methyl amide with (1-dimethylamino)-1-chloro-2-methylprop-1-ene (Ghosez reagent), (-)-thiangazole was obtained in 20% yield from tricycle **22** and in an 0.3% overall yield from L-cysteine **14**.



Scheme 1. The Pattenden synthesis of thiangazole.

In their synthesis of (-)-thiangazole,[19] Parsons and Heathcock prepared (*R*)-α-methylcysteine **27** in 37% yield from D-alanine according to a modification of the Karady procedure (Scheme 3).[2d,29] A series of iterative couplings and deprotections provided tripeptide acid **30**[2d] that was condensed with *O*-benzylthreonine *N*-methylamide by the



Scheme 2. The Ehrler synthesis of thiangazole.

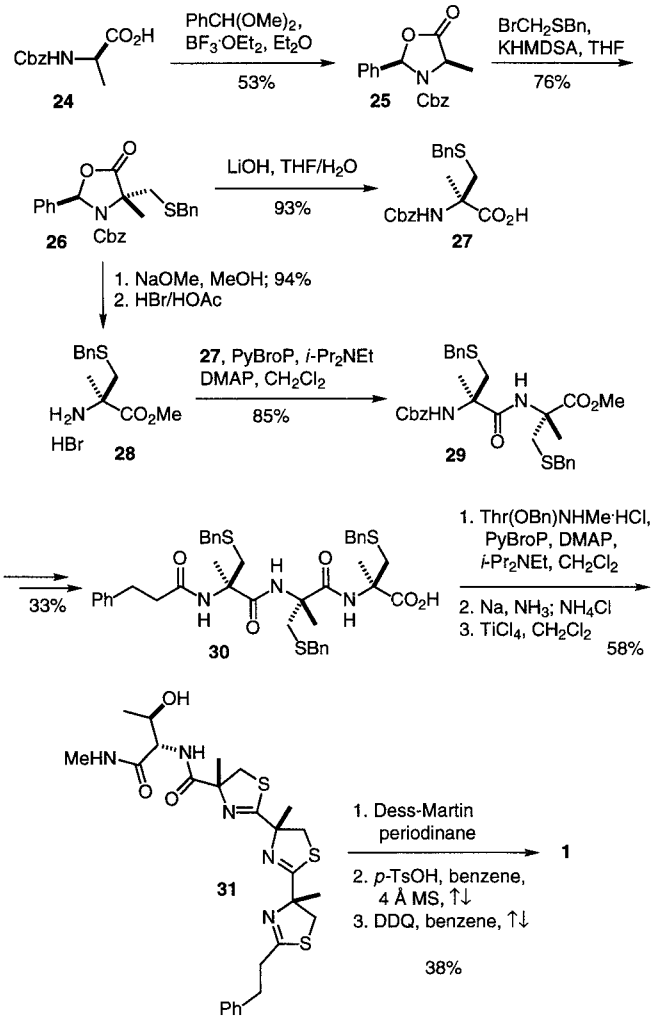
method of Coste et al.[30] After deprotection of the *S*-benzyl ethers, a triple cyclization with $TiCl_4$ in CH_2Cl_2 led to the tris-thiazoline **31**.

The oxazole ring was introduced as the last heterocycle by oxidation with Dess-Martin reagent[31] and cyclodehydration of the resulting β-keto amide with TsOH. The resulting tetracyclic intermediate was converted to thiangazole by side-chain oxidation with DDQ. The overall yield for the longest linear sequence in this synthesis of the *Polyangium* metabolite was 2%.

2. Retrosynthesis and Methodology

In our retrosynthetic approach, we envisioned an efficient access to thiangazole via trisoxazoline **32** that would also serve as a interesting analog of the natural product (Figure 5). After conversion of dipeptide **34** to the terminal oxazole and sequential chain elongation with α-methyl serine and hydrocinnamic acid, triple cyclization of triol **33** would lead to the desired tetrazole intermediate **32**. This retrosynthetic strategy focused heavily on the ready availability of α-methyl serine and on the manipulation of azoles at a late stage of the synthesis. Several new methods had first to be developed to realize these goals.

Due to the high degree of substitution, a synthesis of the oxazole "A" ring analogous to the oxidation of the oxazoline **37** derived from dipeptide **36** was not attractive. Both the NiO_2-[32] and the $CuBr_2$-mediated[28,33] aromatization of C(5)-substituted oxazolines of this type were low-yielding and require long reaction times (Figure 6). We therefore envisioned a modification of this sequence by performing an oxidation prior to cyclodehydration, e.g. **38**→**39**.



Scheme 3. The Heathcock synthesis of thiangazole.

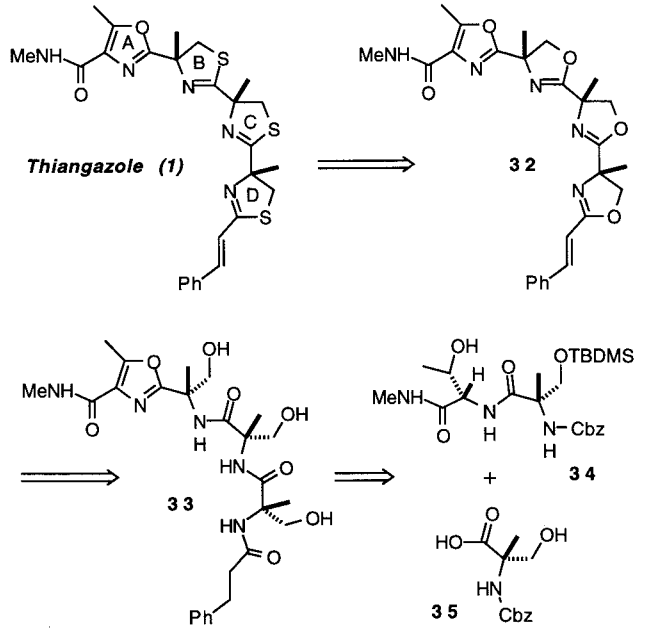


Figure 5. Retrosynthetic Approach.

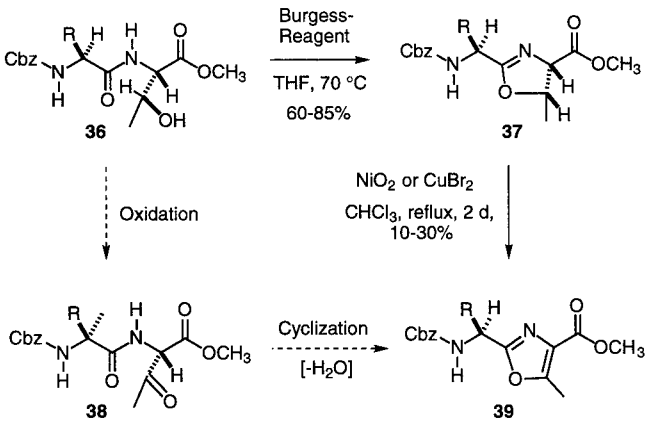


Figure 6. Synthesis of per-substituted oxazoles.

The conversion of keto amides to oxazoles had already been realized by Robinson in 1909,[34] however, the reagents that were generally used in this reaction (e.g. conc. H_2SO_4, PCl_5, $SOCl_2$, and others[35]) were not compatible with the functionality present in peptide derivatives. In situ prepared electrophilic phosphorus reagents[36] appeared more promising, and side-chain oxidation of peptide **36** with the highly selective Dess-Martin periodinane reagent[31] **41** should provide a viable access to the sensitive ketone. Indeed, this modification of the Robinson-Gabriel synthesis employing Dess-Martin oxidation and cyclodehydration with triphenylphosphine/iodine proved to be highly

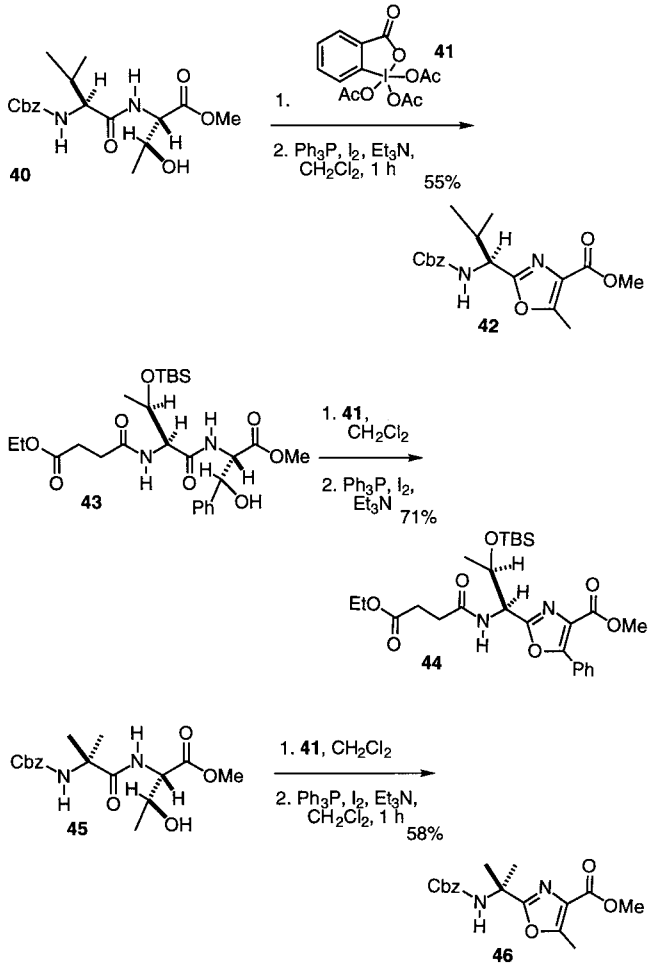


Figure 7. Modified Robinson-Gabriel synthesis of peptide oxazoles.

successful not only for the preparation of the A-ring of thiangazole but also for the general synthesis of peptide oxazoles (Figure 7).[37] Mechanistically, these reactions probably involve intermediate carbenes **49** (Figure 8).[37,38]

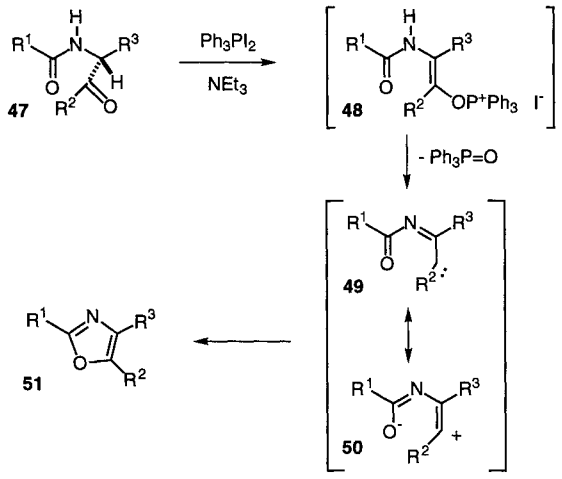
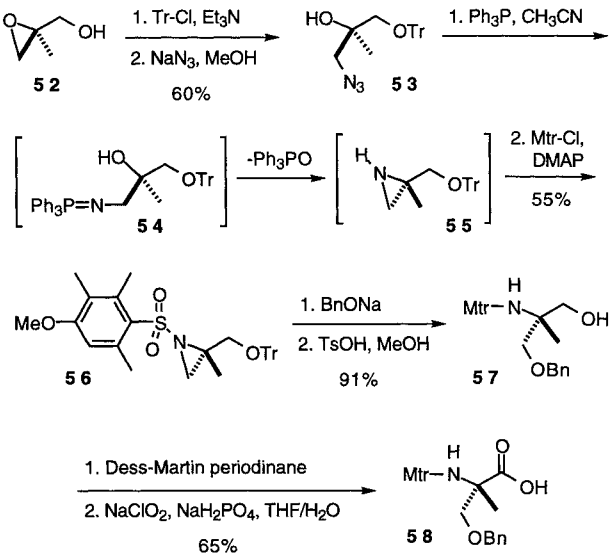


Figure 8. Proposed mechanism for cyclodehydration of keto amides **47**.

The repetitive use of α-methyl serine in the assembly of the thiangazole backbone structure required a considerable supply of suitably protected derivatives of this non-proteinogenic amino acid. Even though several protocols for the synthesis of α-methyl serine were available,[39] these methods generally provided unprotected or monoprotected amino acid. Especially in the case of a trifunctionalized amino acid such as α-methylserine, the introduction of protective groups suitable for further transformations in the context of a total synthesis generally requires several additional steps. Therefore, we were interested in an efficient stereoselective approach to fully protected α-methylserine that would be directly useful for our thiangazole synthesis. Such a procedure was realized by the concise conversion of methyl glycidol into *N*-sulfonyl,*O*-Bn-protected α-methylserine (Scheme 4).[40] The Staudinger reaction of azide **53** effected the direct conversion to the aziridine **55** via intramolecular cyclodehydration of imine **54**,[41] and in situ *N*-sulfonylation with 2,3,6-trimethyl-4-methoxybenzenesulfonyl chloride (Mtr-Cl)[42] gave activated aziridine **56**. Selective nucleophilic ring-opening at the less-substituted position of **56** occurs with a range of nucleophiles, but a suitably protected derivative was obtained by the use of sodium benzyloxide, and di-protected α-methyl serine **58** was prepared in an overall yield of 20% after oxidation of **57**.[43] In the actual synthesis of thiangazole, Mtr-Cl was replaced by β-trimethylsilylethanesulfonylchloride (Ses-Cl),[44] which is more easily removed in the presence of amide functions (*vide infra*). Scale-up of this sequence was readily accomplished, and sufficient quantities of both (*S*)- and (*R*)-α-methylserine building blocks were obtained for further use in total synthesis.



Scheme 4. Synthesis of α-methylserine from methyl glycidol.

The conversion of tris-oxazoline **32** to the tris-thiazoline functionality present in thiangazole probably represented the most ambitious step of our proposed synthetic strategy. We envisioned two possible pathways. Thiolysis at C(2) should, analogous to the hydrolysis sequence,[45] provide thioamides **60** that could be converted to thiazolines by cyclodehydration with Burgess reagent[46] or under Mitsunobu conditions (Figure 9).[47] Alternatively, opening at C(5) would provide a cysteine derivative **62** that was also convertible to the desired thiazoline **61**.[48] Limited but encouraging precedence for C(2)- as well as C(5)-opening of oxazolines with sulfur nucleophiles was found in the conversions of **64** to **65**[49] and **66**[50] (Figure 10). However, the regioselectivity as well as the feasibility of these opening reactions on more highly substituted substrates was not clear.

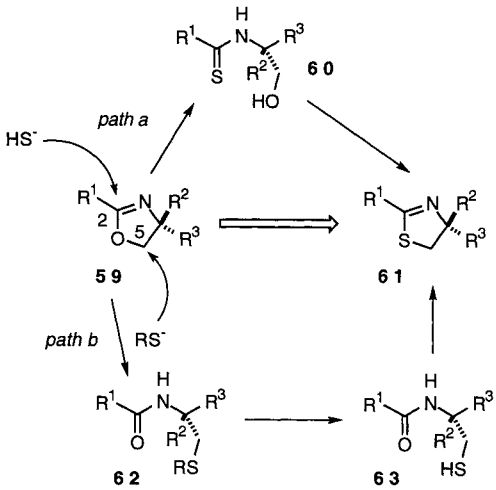


Figure 9. Possible pathways for the conversion of oxazolines into thiazolines.

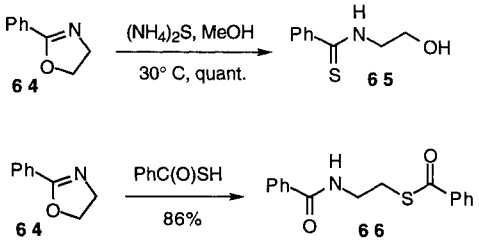


Figure 10. Precedence for C(2)- and C(5)-opening of oxazolines.

Indeed, we found that the success of pathway *a* depended on the reaction conditions during thiolysis. A mixture of H_2S-saturated ammonia in methanol was not compatible with ester functions, and reactions were quite sluggish with substituted oxazolines. Mixtures of triethylamine and methanol in ratios of 1:1 to 1:10 were more promising, whereas all attempts to replace gaseous hydrogen sulfide with sulfide salts or silylated derivatives such as TMS-SH[51] met with failure. The control of the pH of the reaction mixture, as influenced by the selection

of the amine component, was quite crucial for the outcome of the thiolysis. In the model reaction shown in Figure 11, the use of more basic reaction conditions led to the formation of C(5)-opened oxazoline.

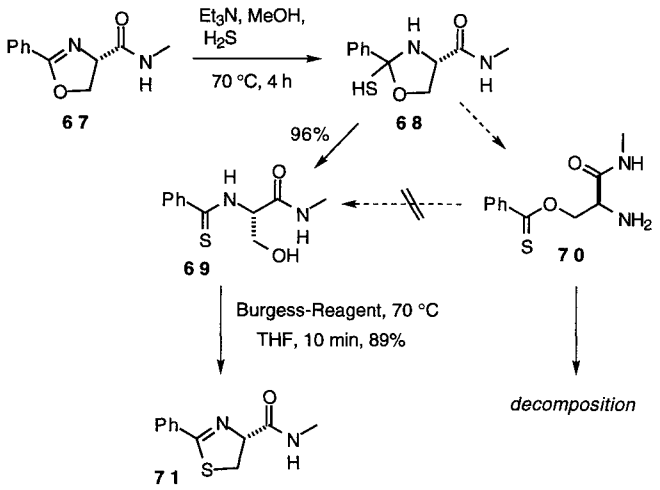


Figure 11. Model system for oxazoline→thiazoline conversion.

Under more acidic reaction conditions, initial attack by sulfur occurred at C(2), but the tetrahedral intermediate **68** decomposed preferentially via C-N bond cleavage, and the isolation of the resulting thionoester **70** proved elusive. Under optimal conditions, however, the desired thioamide **69** was isolated in quantitative yield, and subsequent exposure to Burgess reagent provided thiazoline **71** in a two-step overall efficiency of 85%. More importantly, this reaction was readily transferable to a wide range of peptide oxazolines and essentially free of racemization (Figure 12).[52,53]

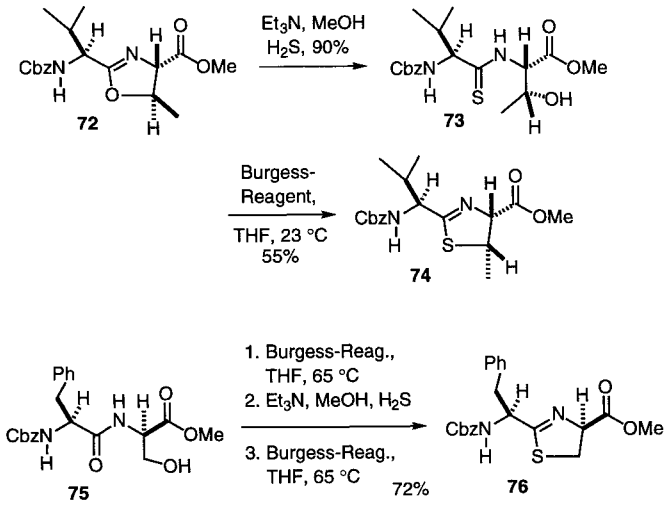


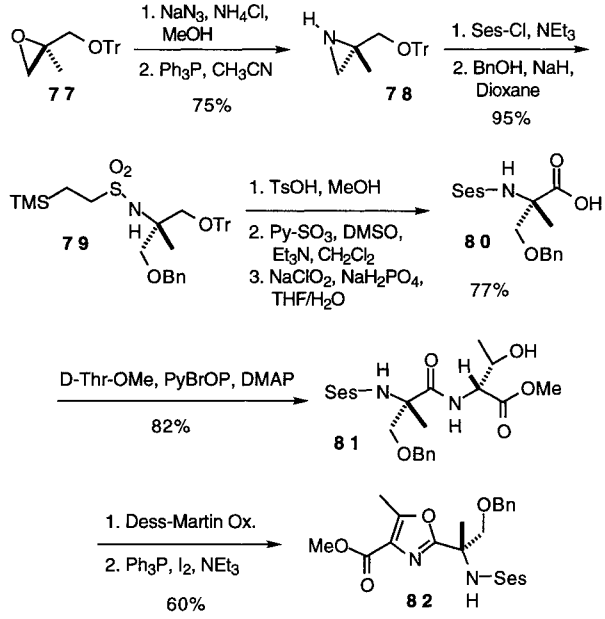
Figure 12. A general method for oxazoline→thiazoline conversion.

3. Total Synthesis of (-)-Thiangazole

In the extended methodology phase prior to the start of the total synthesis of thiangazole, we had been successful in addressing several of the key features in our envisioned synthetic strategy toward the natural product:

- an efficient synthesis of highly substituted oxazoles from peptide precursors,
- the large-scale preparation of (*S*)- and (*R*)-α-methylserine segments with protective groups that fit tightly into our retrosynthetic strategy, and
- a mild and high-yielding oxazoline→thiazoline conversion via thioamides.

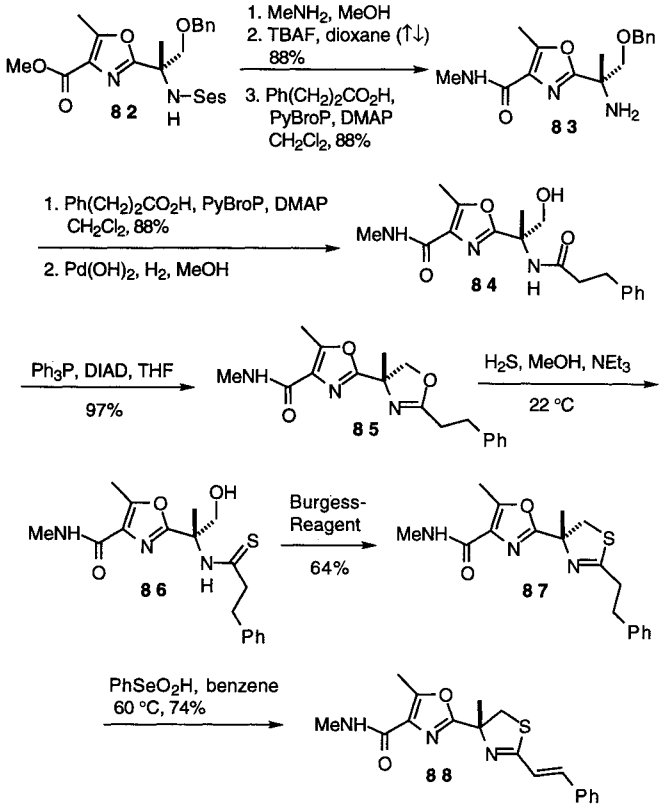
We now faced the challenge, but also the opportunity, to apply these new methods toward an efficient total synthesis of the complex natural product. Treatment of methyl glycidol **77** with sodium azide and *in situ* Staudinger reaction and cyclization gave aziridine **78** in 75% yield and >92% enantiomeric excess (Scheme 5).[40] *N*-protection and activation was achieved by condensation of the amine with Ses-Cl, which allowed the smooth ring-opening with alcoholate nucleophiles. Other N-protective groups such as amides or carbamates suffered from deacylation under these reaction conditions and/or were difficult to remove in later stages of the synthesis. After conversion of the protected primary alcohol in **79** to the carboxylic acid **80**, coupling with D-threonine methyl ester in the presence of PyBroP[30] and DMAP gave the dipeptide **81** in 82% yield. Since the threonine α– and β-stereocenters are destroyed in the subsequent conversion of **81** to the oxazole **82**, L- and D,L-threonine can also be employed in this coupling. However, the use of L-threonine methyl ester led to ca. 10-15% lower coupling yields and decreased reaction rates with (*S*)-**80**, probably due to more unfavorable steric interactions in the diastereomeric transition state for the acylation with the highly hindered acid.



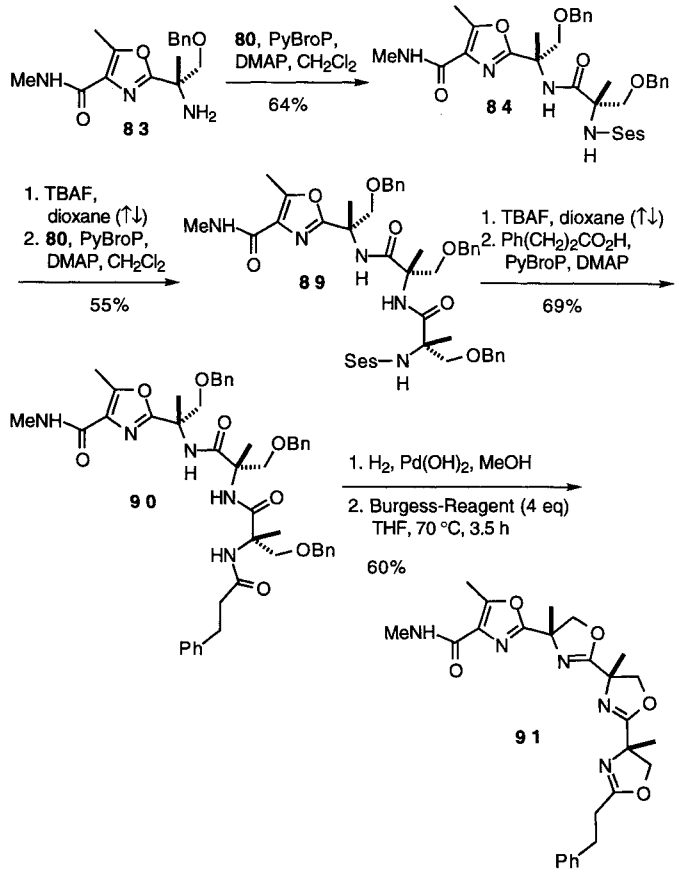
Scheme 5. Synthesis of the A ring system of (-)-thiangazole.

Oxazole synthesis via side-chain Dess-Martin oxidation and cyclodehydration of dipeptide **81** with triphenylphosphine/iodine[37] provided the highly functionalized oxazole **82** in 60% yield. After aminolysis of the C-terminal methyl ester, deprotection of Ses was readily accomplished by treatment with TBAF in anhydrous dioxane to give amine **83** (Scheme 6). In order to test the planned oxazoline→thiazoline conversion on an example relevant to the natural product, amine **83** was acylated with hydrocinnamic acid and the benzyl ether was cleaved by catalytic hydrogenation.

The resulting alcohol **84** was cyclodehydrated with Burgess reagent[46] or under Mitsunobu conditions[47] to give oxazoline **85** that readily succumbed to thiolysis under standard conditions[52] to give thioamide **86**. Renewed exposure to Burgess reagent provided the A-B oxazole-thiazoline fragment of thiangazole in good overall yield. Oxidation of the phenethyl side chain to the styryl function was accomplished with several reagents, including DDQ. Highest yields for this transformation were obtained with the Barton protocol using benzeneseleninic acid at 60 °C.[54]



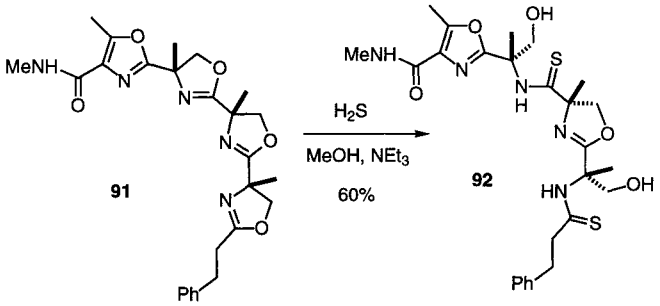
Scheme 6. Synthesis of the A-B ring system of thiangazole.



Scheme 7. Synthesis of the tris-oxazoline thiangazole analog **91**.

The synthesis of the A-B ring system of thiangazole served as a proof of concept for the feasibility of our methodology and synthetic strategy. An extension toward the total synthesis of the natural product now appeared straightforward. In a series of PyBrOP-mediated couplings with **80** and dihydrocinnamic acid, the N-terminus of **83** was extended to give the tetrapeptide **90** (Scheme 7). Oxazole **90** was isolated in 6% overall yield from methyl glycidol **77**. Much to our delight, simultaneous removal of the benzylether groups in **90** followed by triple cyclization with excess Burgess-reagent provided the desired trisoxazoline analog of thiangazole in 60% yield.

The next step in our sequence was the planned triple thiolysis of **91**. At this point, however, the increased steric hindrance especially in the C-ring heterocycle which is flanked by two quarternary centers became insurmountable for our oxazoline-thiolysis protocol (Scheme 8). Under a variety of conditions such as increased temperature and H_2S-pressures, only B- and D-ring oxazolines were converted to the corresponding thioamides **92**. In addition to the steric hindrance argument, the presence of the electron-withdrawing B-ring-derived thioamide function could also be responsible for the observed lack of reactivity of the C-ring, since the oxazoline nitrogen in **92** might not be sufficiently basic anymore to become protonated and activated under the reaction conditions. The addition of stronger acid, however, led to a rapid decomposition of both **91** and **92**.

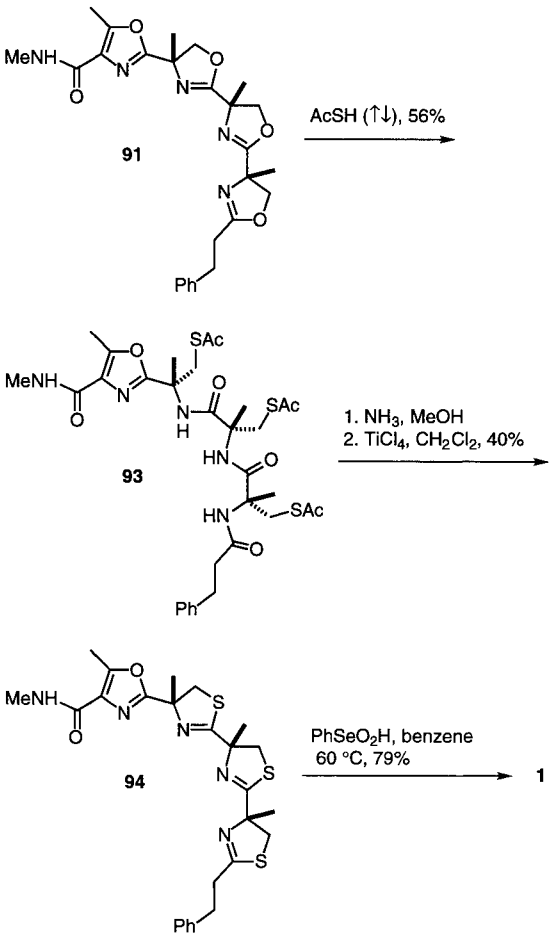


Scheme 8. Incomplete thiolysis of the trisoxazoline intermediate **91**.

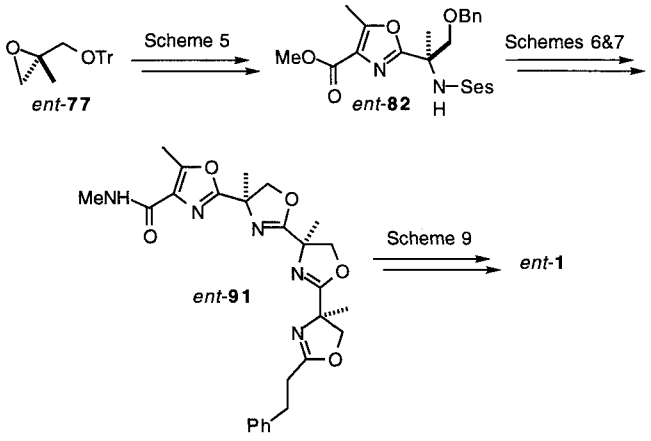
In spite of the valiant efforts by Srikanth Venkatraman, the fourth-year graduate student in charge of the thiangazole synthesis, we were unable to develop reaction conditions for the desired triple thiolysis of **91**. Therefore, we directed our attention to pathway *b* in Figure 9, e.g. the C(5)-opening of oxazolines with sulfur nucleophiles. Indeed, exposure of **91** to neat thiolacetic acid provided the α-methylcysteine derivative **93** in 56% yield (Scheme 9). The acetate groups were readily removed by aminolysis in methanol. The resulting unstable tristhiol was immediately cyclodehydrated according to Heathcock's protocol with $TiCl_4$[2d] to give the tristhiazoline **94**. After this successful oxazoline→thiazoline conversion, (-)-thiangazole (**1**) was obtained by side-chain dehydrogenation with benzeneseleninic acid. Synthetic **1**, which was obtained in 21 steps and an overall yield of 0.6% from methyl glycidol **77**, was spectroscopically and chromatographically identical to a sample of the natural compound[14] that was kindly provided by Jansen et al.

In an analogous fashion, (+)-thiangazole, *ent*-**1**, was prepared from (*R*)-α-methylglycidol *ent*-**77** (Scheme 10).

With the completion of the total syntheses of (-)- and (+)-thiangazole, we had been able to realize our original retrosynthetic approach and to demonstrate the efficiency of our new methodology, e.g. the conversion of aziridines into amino acid segments, the synthesis of highly substituted oxazoles from β-hydroxyamides, and the oxazoline→thiazoline transmutation, for the preparation of heterocyclic natural products. The use of α-methylserine rather than α-methylcysteine amino acid building blocks considerably facilitated the preparation of the multiple linked heterocycles found in thiangazole and provided maximum flexibility for analog syntheses. Similarly, oxazoline isosteres of the sulfur-containing natural product obtained in the course of our synthesis represented attractive first-generation analogs. The structure-activity study of (-)-thiangazole became even more urgent as we detected a high



Scheme 9. Total synthesis of (-)-thiangazole.

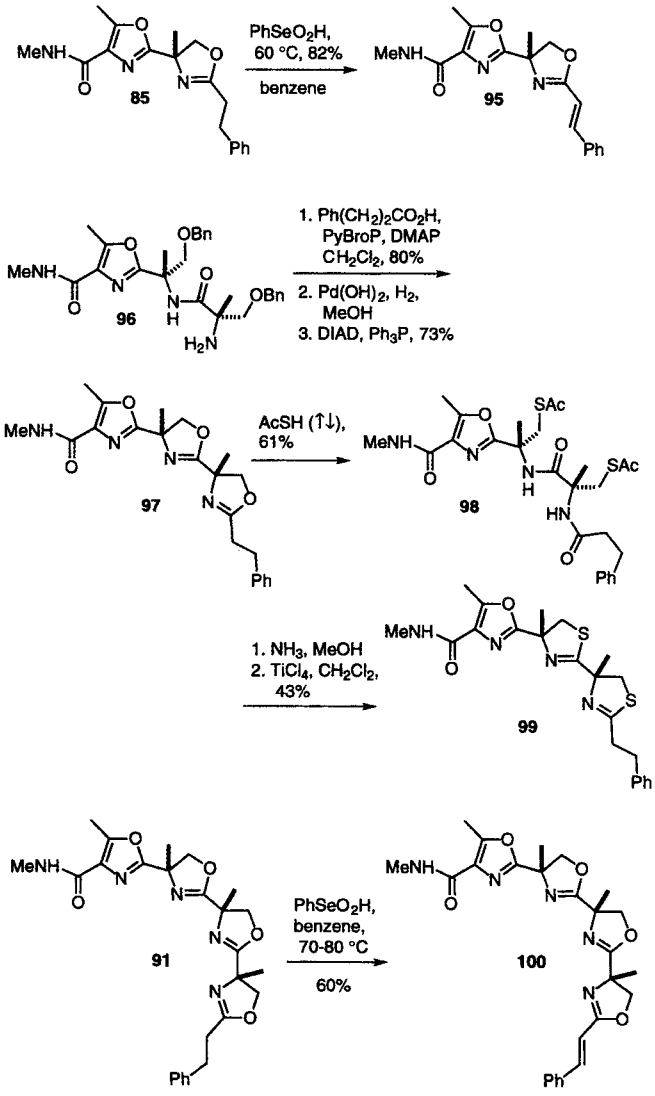


Scheme 10. Total synthesis of (+)-thiangazole.

level of cytotoxicity of the natural product, contrary to the published[14,15,16,21] results. In our preliminary biological analyses,[55] the exceptionally low TD_{50} of 0.003 μM observed for thiangazole in CEM-T_4 and H9 cells obscured any potential anti-HIV-1 activity. We hoped that replacement of thiazolines with oxazoline heterocycles would lead to a decrease of the general toxicity of the compound without seriously interfering with the hopefully more specific antiviral effects.

4. Synthesis of Thiangazole Analogs

In addition to the side-chain saturated analogs **91** and **94**, several additional derivatives of our synthetic intermediates were readily accessible by dehydrogenation or thiolysis of intermediates of the synthetic pathway (Scheme 11). The evaluation of the antiviral effects of these analogs is still in progress. As expected, however, we observed large differences in the toxicity of oxazoline and thiazoline-containing derivatives. The level of cytotoxicity in human breast cancer cells for the oxazoline analog **100**, for example, was lower by at least a factor of 10^3 vs. the natural product (Table 1). Most remarkable, however, was the difference that we observed between (natural) (-)-thiangazole and the synthetic enantiomer (+)-thiangazole which was considerably less toxic![56] We currently do not have any explanation for the biological mechanism that is responsible for this drastically different tolerance for the two enantiomers.



Scheme 11. Analog syntheses.

5. Conclusions

In addition to establishing an efficient new route for the preparation of polyazoles, our studies on the total synthesis of thiangazole have led to the discovery of several new methods in the chemistry of heterocycles that are of general utility. Aziridines are readily prepared by a variety of routes, among others by the azide opening of oxiranes, and are extremely useful for the asymmetric synthesis of nitrogen-containing chiral moieties.[57] Oxazolines are isoelectronic substitutes for thiazolines, and comparison of the pharmacological profile of these five-membered heterocycles can contribute valuable data to structure-activity studies of biologically active compounds. Our retrosynthetic approach to

Table 1.

	(-)-Thiangazole	Trisoxazoline **100**	*ent*-Thiangazole
IC_{50} (MDA-MB-231):	<0.01 μmol	>30 μmol	0.5 μmol

thiangazole had been designed with the intent to expedite SAR studies with oxazoline-containing analogs of the natural product by using them as actual intermediates of the synthetic pathway. In most cases, subsequent conversions of the oxazoline moieties to the corresponding thiazolines via C(2)- or C(5)-openings were realized in > 60% overall yield. As expected, the biological activity, especially the cytotoxicity, of oxazoline-containing compounds is considerably different from the biological profile of the corresponding thiazolines. Beyond the obvious applications in medicinal chemistry, the direct interconversion of heterocycles is of considerable interest for modern heterocyclic chemistry and the total synthesis of heterocyclic natural products, and we are continuing our studies in this important area.

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