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Total Synthesis of (+)-Ileabethoxazole via an Iron-Mediated Pauson–Khand [2 + 2 + 1] Carbocyclization

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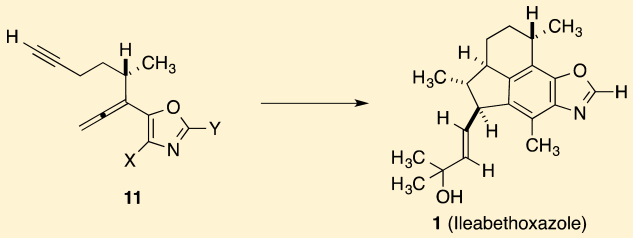
Supporting Information

ABSTRACT: Studies describe the total synthesis of (+)-ileabethoxazole (**1**) using a Stille cross-coupling reaction of propargylic stannanes with 5-iodo-1,3-oxazoles to produce 1,1-disubstituted allenes (**11**). An iron-mediated [2 + 2 + 1] carbocyclization yields a novel cyclopentenone for elaboration to **1**. Site-selective palladium insertion reactions allow for regiocontrolled substitutions of the heterocycle. Asymmetric copper hydride reductions are examined, and strategies for the formation of the central aromatic ring are discussed.



INTRODUCTION

The chemodiversity exhibited by secondary metabolites of the Caribbean octocoral *Pseudopterogorgia elisabethae* has been extensively investigated and has led to the discovery of new carbon skeletons and unusual structural features. A review of selected diterpenes of this family was compiled in 2005 by Heckrodt and Mulzer to summarize the isolation, biosynthesis, pharmacology, and selected synthesis studies.[1] In 2006, Rodriguez and co-workers described the isolation of ileabethoxazole (**1**) (Figure 1) from specimens collected near

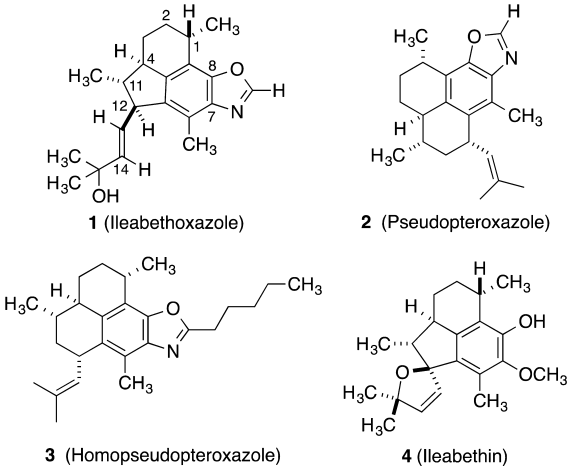


Figure 1. Examples of metabolites of *P. elisabethae*.

the Island of Providencia, Columbia.[2] Ileabethoxazole is a rare example of a marine benzoxazole derived from the serrulatane diterpenoid skeleton by incorporating a subsequent cyclization to produce the fused cyclopentane ring. This metabolite is present in very low concentrations (yield 9.4×10^{-5}% based on dried gorgonian weight), and is structurally similar to pseudopteroxazole (**2**)[3] and homopseudopteroxazole (**3**).[4] After extensive two-dimensional NMR studies, it was concluded that **1** displayed the substituted five-membered ring as described for ileabethin (**4**), which was collected from *P. elisabethae* at a different location.[5] Interestingly, ileabethoxazole (**1**) shows strong inhibition (92%) of *Mycobacterium tuberculosis* ($H_{37}R_v$) (ATCC27294), and this antimycobacterial activity has also been reported for the benzoxazoles **2** (97% inhibition) and **3** (80% inhibition). These substances represent a subset of the family of pseudopterosins, which are widely recognized for their potent anti-inflammatory and analgesic effects.[6,7] The anti-inflammatory activity is of particular interest because the release of pro-inflammatory mediators is suppressed without inhibition of the eicosanoid pathway.[8] More than 30 pseudopterosins have been identified as phenolic diterpenes, which are based on three diastereomeric aglycones connected to various monosaccharides via an acetal linkage.[9] Pseudopterosins A and G are illustrated in Figure 2. Total syntheses of pseudopterosins A[10] and E[11] and several synthesis studies of aglycone diastereomers have been published.[12]

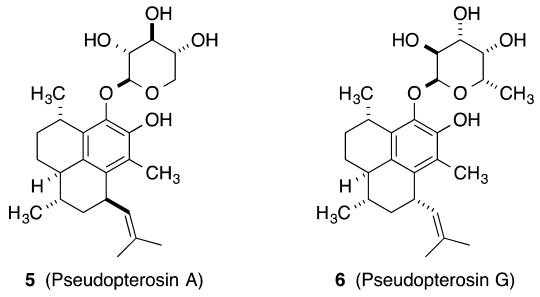


Figure 2. Representative pseudopterosins.

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Our studies have specifically focused on the chemistry of ileabethoxazole (**1**) because of its antitubercular activity. Tuberculosis (TB) continues to be a leading cause of disease-related deaths worldwide. Statistics provided by the World Health Organization (WHO) have documented the significance of the problem.[13] It is estimated that more than 1 billion people are infected. Millions of new cases of TB are diagnosed each year (5.7 million in 2010), and the evolution of new cases of multidrug resistant TB (MDR-TB) have risen dramatically (650 000 in 2010). Drug resistance is a constant threat, and the conditions that allow MDR-TB to re-emerge from dormancy are poorly defined. Selective cytotoxicity toward the slow-growing organism has proven to be a challenging issue.[14] The identification of new lead compounds has been a critical barrier to advances in this arena. Davidson and Corey have reported a synthesis pathway leading to pseudopteroxazole beginning with (*S*)-limonene, and these efforts have also led to a revision of the assigned stereochemistry as depicted in **2**.[15]

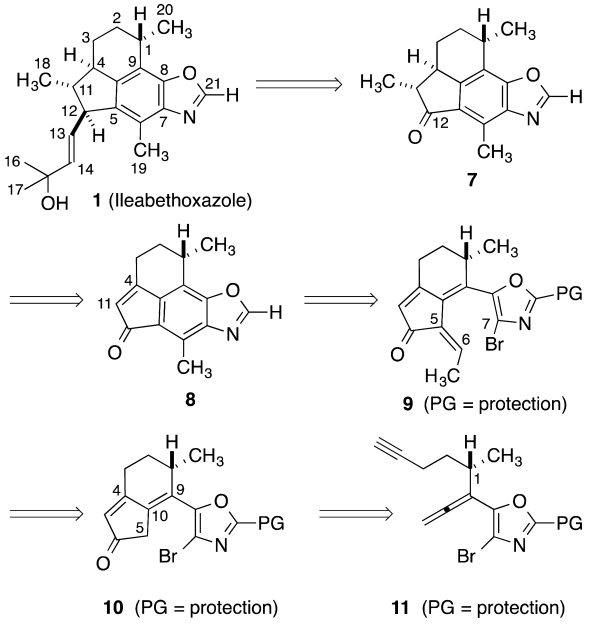
In this work, we describe an enantiocontrolled total synthesis of ileabethoxazole (**1**). Our studies were designed to achieve several specific aims in addition to establishing a viable pathway to the natural product itself. We have sought to provide a synthesis platform for the generation of tricyclic and tetracyclic derivatives of **1** toward studies of medicinal chemistry. We have also explored advancements of synthesis methodology with broad implications. Thus, these efforts feature our findings of palladium-catalyzed cross-coupling reactivity for direct incorporation of the intact oxazole heterocycle. A general and effective preparation of 1,1-disubstutited allenes is described as a prerequisite for the application of a novel iron-mediated [2 + 2 + 1] carbocyclization. Overall, these fundamental advances offer improved efficiency for the assembly of molecular complexity.

RESULTS AND DISCUSSION

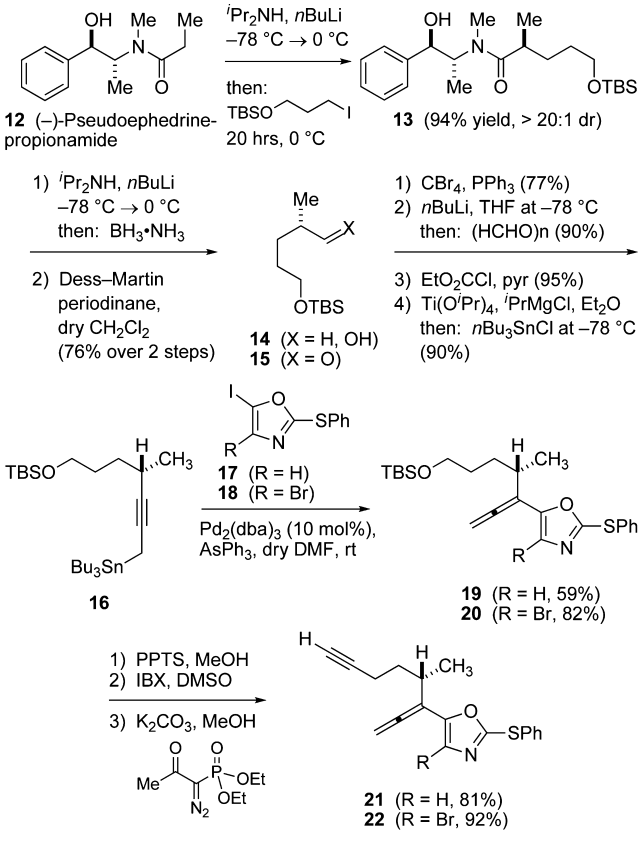
An outline of our synthesis strategy is illustrated in Scheme 1. We envisioned that the *E*-alkenyl chain (C_{13}—C_{17}) of **1** could be introduced via a nucleophilic addition to the C-12 ketone **7** leading to a tertiary benzylic alcohol for reductive deoxygenation. Alternatively, a cuprate reagent, which incorporates the *E*-alkenyl chain, could be used for the displacement of an appropriate benzylic leaving group. The saturated ketone **7** is available by α-methylation of the corresponding enolate, and this transformation is advanced by the conjugate reduction of the enone **8** with subsequent addition of methyl iodide. Since we were interested in opportunities that would directly introduce the oxazole heterocycle, we recognized that **8** could be assembled via the [2 + 2 + 1] carbocyclization of the allene **11** to produce an unsaturated five-membered cyclopentenone **10**. Thus, formation of the fully substituted aromatic ring of **8** is anticipated from an intramolecular Heck reaction of **9**. On the basis of our prior studies of oxazoles, we expected that the C-2 position (C_{21} ileabethoxazole numbering) would be reactive, especially toward hydrogen abstraction or toward nucleophilic additions.[16] This aspect suggested the need to consider a C-2 blocking unit (PG).

Initial studies have explored the development of an efficient method for the preparation of the nonracemic allene **11** of Scheme 1. These investigations have led to the discovery of a regioselective Stille cross coupling reaction of 3-tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne with alkenyl iodides for direct formation of 1,1-disubstituted allenylsilanes.[17] The scope of the reaction is extended to generally include alkyl-substituted propargylic stannanes as illustrated in Scheme 2. The asymmetry at C-1 of ileabethoxazole is introduced by the Myers alkylation[18] of **12**, subsequent reduction of **13**, and Dess–Martin oxidation to provide the nonracemic aldehyde **15**. The asymmetric alkylation gave **13** with high diastereoselectivity (dr $\geq$ 25:1), and this material was purified by flash silica gel

Scheme 1. Retrosynthetic Analysis for Ileabethoxazole (1)



Scheme 2. Preparation of Nonracemic Allenes 21 and 22



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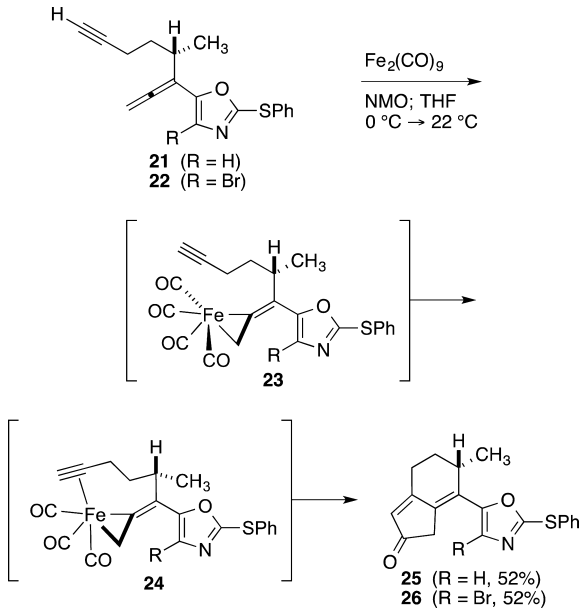
chromatography prior to reduction with lithium amidotrihydroborate.[19] The nonracemic primary alcohol **14** was confirmed by comparison with published characterization data,[20] and its optical purity was also established by Mosher ester analysis.[21] After oxidation to **15**, a small sample of aldehyde was reduced ($NaBH_4$) for an additional Mosher ester analysis, establishing the high optical purity (≥25:1) of **15**. The aldehyde was then utilized for an efficient three-step transformation into the propargylic stannane **16** by application of the Corey–Fuchs procedure, which employed a quench with paraformaldehyde to obtain the corresponding propargylic alcohol.[22] Treatment of this alcohol with ethyl chloroformate and pyridine gave the expected carbonate (95%), and a regioselective, titanium-mediated stannylation exclusively produced the propargyl stannane **16**.[23] This transformation involves a reduction of the starting carbonate by the addition of titanium tetra-isopropoxide and isopropylmagnesium chloride in anhydrous ether at −40 °C. The reaction is quenched by the introduction of tri-*n*-butyltin chloride at −78 °C, and is thought to proceed via the formation of an allenyltitanium intermediate. The stannane **16** is highly acid sensitive and requires flash chromatography using silica gel that has been pretreated with 3% triethylamine in hexanes.

The Stille cross coupling of **16** using 10 mol % $Pd_2(dba)_3$ in dry DMF at 22 °C with oxazoles **17** and **18** proved to be highly regioselective.[24,25] As anticipated, palladium insertion at C-5 leads to the allenes **19** and **20** without formation of enyne products.[17] These experiments do not proceed via an initial isomerization of **16** to the corresponding allenylstannane prior to the cross coupling since substituted allenes are not observed in the absence of the alkenyl iodide coupling partner. The terminal alkynes of **21** and **22** are introduced in three steps by silyl ether hydrolysis, IBX oxidation,[26] and application of the Ohira–Bestmann reagent[27] (81% yield and 92% yield, respectively). In this fashion, Scheme 2 provides a general pathway to readily available substrates for the proposed cyclization studies.

The retrosynthetic analysis suggests opportunities to examine an intramolecular [2 + 2 + 1] carbocyclization to deliver the cyclopentenone system of **10** (Scheme 1). In fact, the Pauson–Khand reaction (PKR) is readily identified as an important process for the synthesis of cyclopentenones via the precomplexation of dicobalt octacarbonyl with an alkyne in the presence of alkene and carbon monoxide at elevated temperatures. Significant contributions by Brummond,[28] Cazes,[29] Evans,[30] and others[31] have improved the scope of the reaction and introduced the use of several transition metal catalysts. Intramolecular variants of the PKR are particularly attractive strategies for the synthesis of polycyclic cyclopentenones in natural product synthesis.[32] The body of published results illustrates successful reactions for relatively unfunctionalized substrates. This aspect raised concerns for our use of allene **22** at elevated pressures and at temperatures exceeding 100 °C. Fortunately, our investigations have uncovered a [2 + 2 + 1] carbocyclization using diiron nonacarbonyl that proceeds under ambient conditions (−20 to 22 °C).[33,34] Studies with 1,1-disubstituted allenylsilanes and a variety of terminal alkynes have demonstrated stereoselective cyclizations leading to (*E*)-4-alkylidene-2-cyclopentenones. Furthermore, these iron-mediated carbocyclizations proved to be tolerant of an impressive range of sensitive functionality. We did not observe reactions with $CO_2(CO)_8$ and $Mo(CO)_6$ under these conditions, and the use of tungsten hexacarbonyl led to poor conversions only in selected cases. We have detailed a mechanistic pathway for these iron-mediated [2 + 2 + 1] reactions which is distinguished from the usual reaction profile of the PKR by the characterization of a reaction-competent, three-membered iron metallacycle.[33] In fact, these reactions are quenched by the introduction of a CO atmosphere. On the basis of these findings, facile carbocyclizations of **21** and **22** occurred in anhydrous THF upon addition of $Fe_2(CO)_9$ and *N*-methylmorpholine-*N*-oxide at 22 °C (Scheme 3). Reactions

Scheme 3. [2 + 2 + 1] Carbocyclizations



progress to the cyclopentenone products at temperatures as low at 0 °C. Our intermolecular studies support the initial formation of the three-membered metallacycle as shown in **23**, followed by oxidative decarboxylation to provide an open coordination site leading to intermediate **24**. Subsequent carbonylation cleanly affords the enones **25** and **26** after purification by flash silica gel chromatography. We speculate that the yields of these isolated enones are somewhat diminished by an accumulation of iron precipitates that may sequester some oxazole product. Without further optimization, at this point, we proceeded to explore formation of the fully substituted aromatic system.

Plans for the synthesis of the central aromatic ring of **1** anticipated the use of a Heck reaction to proceed via palladium insertion into the C_4—Br bond in **26**. Model studies were explored as summarized in Scheme 4 by direct α-methylenation of ketones **25** and **26** to yield the highly unsaturated trienones **27** and **28** using a procedure described by Connell and coworkers.[35] Unfortunately, attempted Heck cyclizations of **28** produce several products upon introduction of the typical palladium catalysts,[36] whereas no reaction of **28** occurs in the presence of $RhCl(PPh_3)_3$ in refluxing toluene.[37] We have also examined the aromatization of **27** as a formal electrocyclization and dehydrogenation with Pd—C, which fails to give the desired benzoxazole **29** as a useful conversion. Mass spectral analyses in these cases suggest adverse reactivity associated with the C-2 phenylthio substituent. In fact, studies by Liebeskind,[38] Guillaumet,[39] and Stambuli[40] have described the metal-catalyzed oxidative insertions in a variety of heteroaromatic

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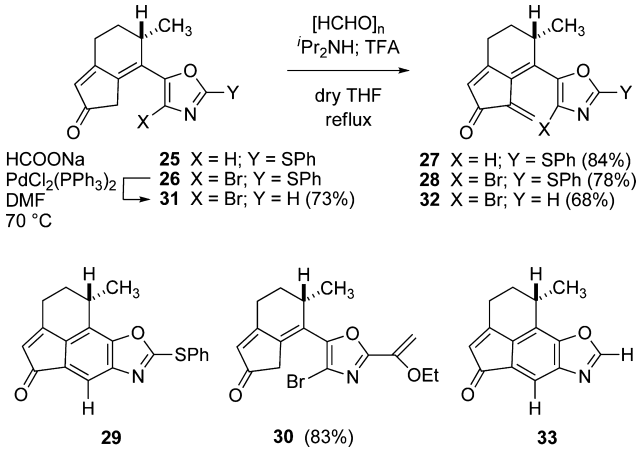
Scheme 4. Attempts for Benzoxazole Formation



thioethers leading to Stille cross-coupling reactions with aryl and alkenylstannanes. Subsequent evidence has confirmed our initial suspicions since the attempts to introduce a methyl ketone equivalent at C-4 of oxazole **26** via a Stille cross-coupling reaction with tri-*n*-butyl(1-ethoxyvinyl)tin using $PdCl_2(PPh_3)_2$ in THF at 67 °C exclusively gave **30** (83% yield). This selective oxidative insertion into the C-2 carbon—sulfur bond in the presence of the C-4 bromide provides a useful pattern of reactivity for substitution reactions of the oxazole nucleus. The observed relative rates of palladium insertion reactions are portrayed in Figure 3.

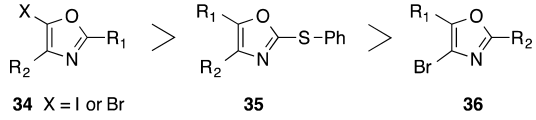
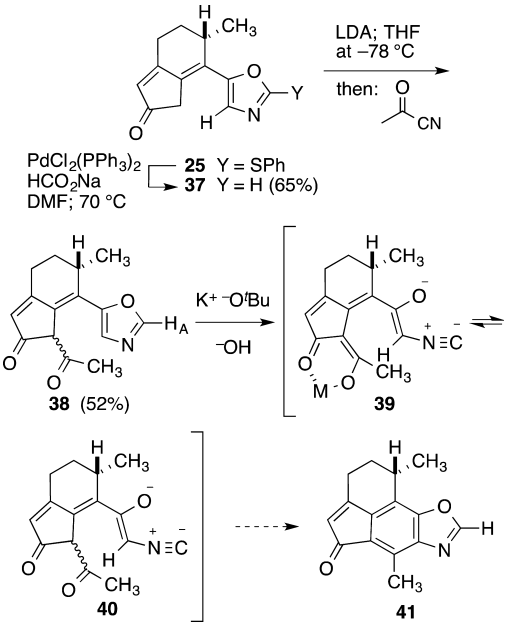


Figure 3. Relative reactivity of cross-coupling reactions.

The results show that insertion for C-5 iodides and bromides of **34** is considerably faster than the rate of C—S bond insertion of C-2 thioethers **35**. Reactions of the C-4 bromides **36** are much slower, albeit feasible.[25] Prior efforts of Liebeskind and Neumann[41] suggest that it may be possible to alter this reactivity pattern by the choice of the palladium catalyst and/or various additives. On the basis of these observations, a selective reduction of **26** with sodium formate and $PdCl_2(PPh_3)_2$ gave oxazole **31** (73%) which led to α-methylenation affording **32** (68%). However, the proposed intramolecular Heck reaction of **32** to yield **33** also provided a substantial number of byproducts.

Concomitant with these efforts, our studies of a carbonyl condensation strategy were initiated toward construction of the aromatic system. As illustrated in Scheme 5, the reduction of the C-2 phenylthio ether of **25** gave the expected conjugated ketone **37**. Deprotonation of **37** with LDA (1.0 equiv) in THF at −78 °C led to C-acylation using acetyl cyanide (pyruvonitrile). Our studies of the diastereomeric mixture of 1,3-diketones **38** sought a base-promoted equilibration of enolates featuring the ring-opened tautomers **39** and **40** as significant intermediates for the internal condensation to produce **41**. In these attempts, our failures were met with the recovery of the starting 1,3-diketone. However, the base-induced deprotonation of oxazole **32** (from Scheme 4) was also

Scheme 5. Carbonyl-Condensation Strategy Toward 41



examined as an opportunity for an intramolecular Michael reaction, and this exercise rapidly led to decomposition.

The accumulated evidence from these studies led to alterations of our synthesis plan with two significant adjustments. First, the base-induced aromatization can be most advantageously accomplished by installation of a methyl ketone at C-4 of the oxazole heterocycle, and this moiety must be incorporated at an early stage. Second, the reactivity of the C-2 phenylthio ether toward palladium insertion proved problematic. This aspect can be eliminated by oxidation to the corresponding sulfone. However, we have previously observed facile nucleophilic substitution reactions of related 2-sulfonyl-1,3-oxazoles.[42] With this in mind, the trialkylsilyl substituent was selected as an appropriate C-2 blocking unit. These changes require validation for the key reactions demonstrating allene preparation as well as the subsequent [2 + 2 + 1] cyclization.

An effective pathway for synthesis of the requisite allene is shown in Scheme 6, beginning with commercially available ethyl-1,3-oxazole-4-carboxylate via conversion to the Weinreb amide **43** for addition of methylmagnesium bromide. The resulting C-4 methyl ketone is transformed into the corresponding methoxymethyl (MOM) ether **44**, and sequential ring metalations at C-2 and C-5 by regioselective deprotonations with LDA in THF lead to the desired iodide **45**. The Stille cross coupling of **45** with the propargylic stannane **16** (from Scheme 2) proceeds with allylic transposition to give the allene **46** in good yield (76%) following purification by flash chromatography. Removal of silyl protecting groups is accomplished upon stirring in methanol with pyridinium tosylate (PPTs) at 22 °C, and the alkyne of **47** is introduced by oxidation and application of the Ohira−Bestmann procedure.[27] The iron-mediated [2 + 2 + 1] carbocyclization of **47** (Scheme 7) proceeds in THF upon warming from −50 to 5 °C, and affords the expected dienone **48** (61% yield). Cyclization and aromatization is efficiently achieved by cleavage of the MOM acetal of **48**, Swern oxidation, and subsequent treatment with potassium *tert*-butoxide (2.4 equiv) in dry toluene at −20 °C to afford desired enone **41** (93% yield) as a

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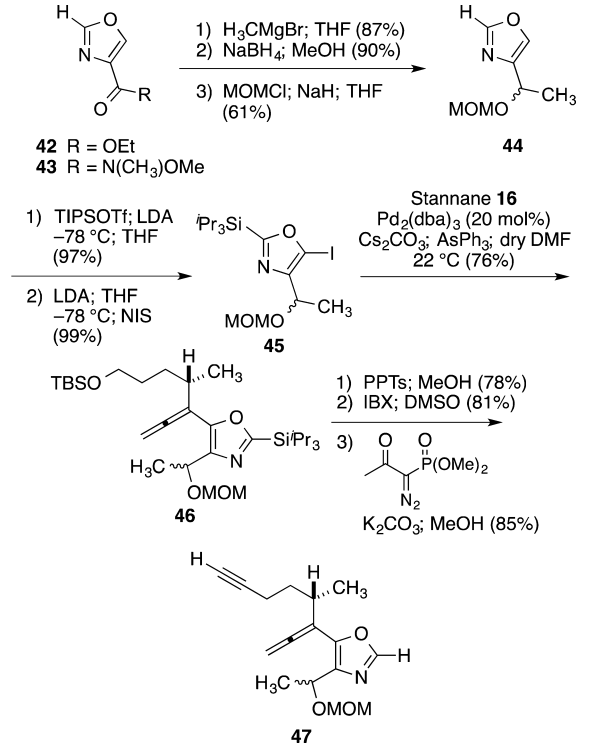
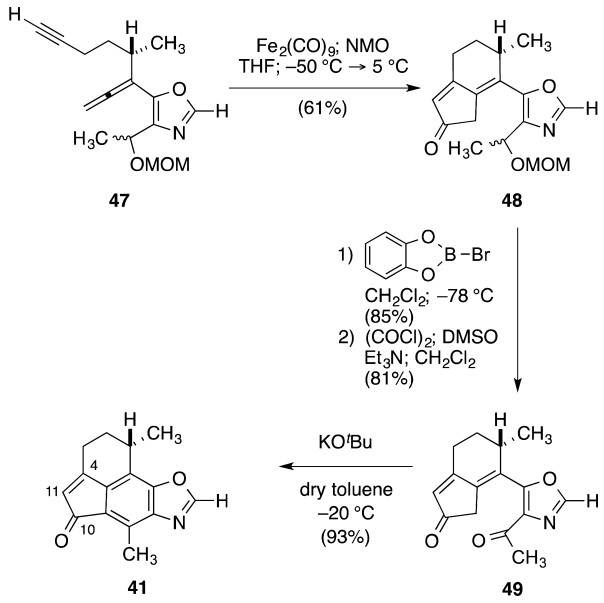
Scheme 6. Preparation of Allene 47



Scheme 7. Formation of the Tetracyclic Benzoxazole 41



solid (mp 92−94 °C). Isomerization of **41** is observed to provide the corresponding β,γ-enone upon flash chromatography with silica gel that has been pretreated with 3% triethylamine in hexanes.

Fortunately, this double-bond migration is completely avoided under the usual conditions of flash chromatography, and this observation simplified subsequent plans for reduction and methylation of ketone **41**. We sought to achieve facial stereoselectivity via a reagent-controlled reduction of the conjugated enone by employing a chiral hydridocopper species. Initial experiments examined a one-pot protocol of Buchwald and co-workers,[43] and found that the anticipated copper hydride conjugate addition occurred with minimal yields of in situ α-methylation. The stereoselectivity of the 1,4-reduction of **41** has been studied as summarized by the survey of results in Table 1. In fact, facile reductions take place at 20 °C in the presence of Ph_2SiH_2, CuCl (20 mol %), and the nonracemic (*S*)-pTol-BINAP ligand (20 mol %) to produce diastereomers **50** and **51** (dr 75:25) in 87% combined yield (entry 1). The integration of selected signals in the proton NMR spectra of the reaction products provided isomer ratios which were generally confirmed by subsequent HPLC analysis. For example, signals for the oxazole C_2—H at δ 8.08 (**50**) and δ 8.07 (**51**) in combination with the doublet of the C—CH_3 at δ 1.54 (**50**) and δ 1.34 (**51**) were measured with consistency. We note that the observed diastereoselectivity is slightly diminished as the reaction temperature is decreased (entries 1−3). Furthermore, the reaction at −55 °C (entry 3), resulting in the production of **50**/**51** (dr 61:39), is also complicated by carbonyl reduction of these products leading to poor yields. The use of the DTBM-(*S*)-SEGPHOS hydridocopper species[44] (entry 4) using polymethylhydrosiloxane affords slow reactions with considerable formation of the corresponding allylic alcohols by 1,2-reduction. Interestingly, the generation of the (*S*)-SEGPHOS hydridocopper complex using Ph_2SiH_2 improved the diastereoselectivity and the yield of the reduction (entry 5).

The conversion to **50** is optimized by the use of (*S*)-H_8-BINAP (20 mol %) and Ph_2SiH_2 at 20 °C (entry 6). This modification proceeds with good stereocontrol (dr 86:14) and avoids the formation of side products. For comparison, the diastereoselectivity of the catalytic hydrogenation of **41** with 5% Pd—C (entry 7) and reduction with lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB)[45] (entry 8) favored formation of the undesired **51**.

Transformation of the purified **50** to the corresponding C-11 methyl ketone **52** via alkylation with methyl iodide is characterized by poor yields of the expected product (<15%) and the recovery of starting material. Deprotonation of **50** with LHMDS (2.2 equiv) in THF at −78 °C followed by a deuterium quench (D_2O) provides evidence of complete exchange of the C_2—H of the oxazole ring and minimally 90% incorporation of a single deuterium at the α-methylene. The lithium enolate derived from **50** is surprisingly unreactive at low temperatures, in spite of the inclusion of the usual solvent additives (HMPA and DMPU). This problem is resolved by α-methylenation using *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane[46] and acetic anhydride, and subsequent reduction as described by Lipshutz and co-workers using in situ (BDP)CuH reagent.[47] In this fashion, the α-methyl ketone **52** is produced in 76% yield as a white waxy solid (mp 142−150 °C). The product is isolated as a single diastereomer, and the relative stereochemistry at C_4 and C_{11} is recognized by NOESY correlations of the C_4—H (δ 2.71−2.80 (m)) with the C_{11}-methyl substituent at δ 1.35 (d) as well as the C_1-methyl group at δ 1.55 (d). These findings mirrored similar correlations described for the natural product itself. The side chain component of **1** is readily prepared from 3-methyl-1-butyn-3-ol via palladium-catalyzed hydrostannation to give the known (*E*)-alkenylstannane,[48] followed by TBS silyl ether formation. Initial conversion to the known (*E*)-iodide **53**,[49] using iodine in CH_2Cl_2 at 0 °C, affords a cleaner transmetalation with *n*-butyllithium (Scheme 8), and the corresponding alkenyllithium species leads to carbonyl addition for synthesis of the C-12 tertiary alcohol **54** (70% yield). However, experiments to provide for an effective deoxygenation of **54** are characterized

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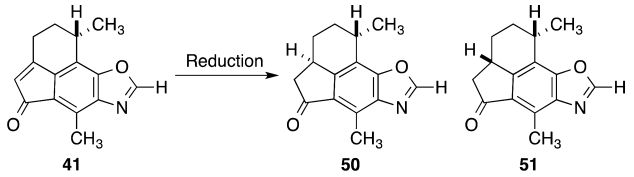
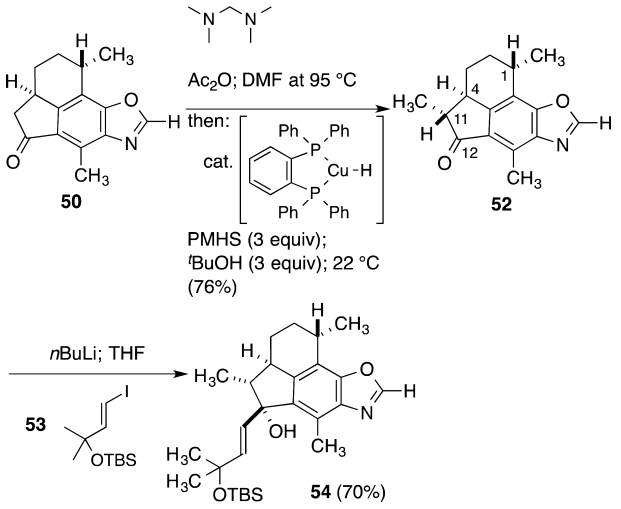
Table 1. Conjugate Reductions of Enone 41



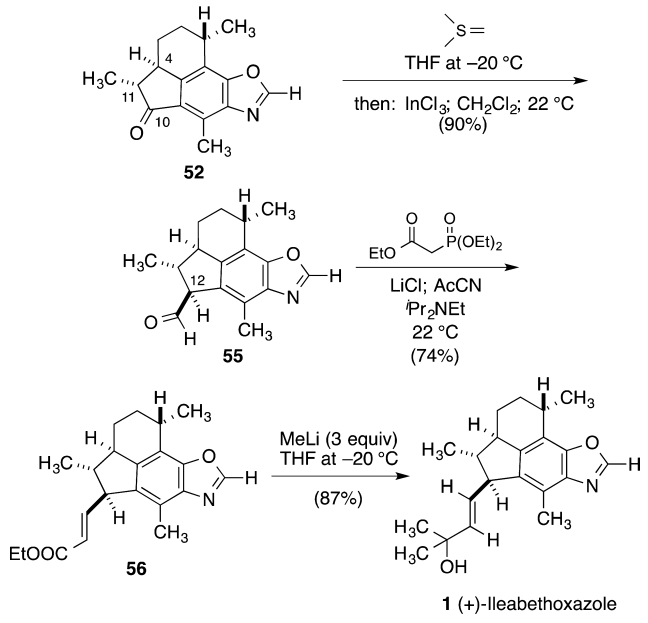
entry	conditions	dr (50/51)	% yield
1	conditions[a] at 20 °C (3 h) (*S*)-pTol-BINAP (20 mol %)	75:25	87
2	conditions[a] at −30 °C (3 h) (*S*)-pTol-BINAP (20 mol %)	67:33	78
3	conditions[a] at −55 °C (3 h) (*S*)-pTol-BINAP (20 mol %)	61:39	≤40[c]
4	conditions[b] at −30 to 0 °C (24 h) (*S*)-DTBM-SEGPHOS (20 mol %)	ND[e]	≤30[d]
5	conditions[a] at 20 °C (3 h) (*S*)-SEGPHOS (20 mol %)	78:22	85
6	conditions[a] at 20 °C (3 h) (*S*)-H_8-BINAP (20 mol %)	86:14	79
7	H_2 (1 atm); 5% Pd−C	33:67	93
8	LiDBB (10 equiv); THF bis(methoxyethyl)amine (1.3 equiv) at −78 to −30 °C	25:75	61

[a]CuCl (20 mol %); NaO^{t}Bu (20 mol %); Ph_2SiH_2 (0.53 equiv); ligand in toluene. [b]CuCl (20 mol %); NaO^{t}Bu (20 mol %); PMHS (1.2 equiv); ligand in toluene. [c]Varying amounts of isomeric α/β-alcohols from **50**/**51** are also obtained. [d]Rapid C=O reduction gives mixtures of allylic alcohols and **50**/**51** with modest conversions; [e]Not determined.

Scheme 8. Introduction of C_{11} and C_{12} Substitution in Ketone 50



Scheme 9. Completion of the Synthesis of (+)-Ileabethoxazole (1)



by poor yields in the attempts to transform the hindered alcohol into a preferred derivative for nBu$_3$SnH reduction. Furthermore, subsequent attempts for Barton deoxygenation of small amounts of thione derivatives also led to unexpected complications, as evidenced by the isolation of products arising from reduction of the C=C moiety and loss of the OTBS substituent.

Finally, the total synthesis of (+)-ileabethoxazole (**1**) is completed in three efficient operations, as illustrated in Scheme 9. Treatment of **52** with methylenedimethylsulfurane at −20 °C yields an intermediate epoxide which undergoes facile rearrangement in the presence of anhydrous $InCl_3$.[50] The aldehyde **55** is produced as a single isomer as a result of epimerization at C-12, and application of the Horner−Emmons reaction[51] results in formation of the stable α,β-unsaturated ethyl ester **56**. The subsequent addition of methyllithium (3 equiv) leads to synthetic (+)-ileabethoxazole (**1**), which has been shown to be identical in all respects, including optical rotation (α^{22}D + 9.3° (c 1.50, $CHCl_3$), with characterization data provided for the natural product.[2]

In summary, the first synthesis of (+)-ileabethoxazole (**1**), a novel inhibitor of *Mycobacterium tuberculosis*, has been described. Key features of our investigation include the effective preparation of 1,1-disubstituted allenes via a Stille cross coupling of propargylic stannanes. Our studies have reported useful aspects of the relative reactivity for cross-coupling processes at the C_2, C_4, and C_5 positions of the oxazole nucleus. An exceptionally mild, iron-mediated [2 + 2 + 1] carbocyclization has been documented. Our intramolecular PKR variant using inexpensive $Fe_2(CO)_9$ tolerates a wide variety of functionality, notably including the heterocyclic amine. These reactions proceed via the reactivity of a previously unexplored three-membered iron metallacycle. A slight modification that introduces the use of the chiral H_8-BINAP ligand in the preparation of hydridocopper reagent for 1,4-conjugate reductions promises improved stereoselectivity in the asymmetric reductions of indenones. Finally, our studies of

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ileabethoxazole have described a pathway well suited for advancements of medicinal chemistry, the generation of focused libraries, and continuing studies to explore the antitubercular activity of these marine natural products.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental description of reactions and characterizations of all new compounds, proton and carbon NMR spectra, as well as comparison data of synthetic and natural ileabethoxazole. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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