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Total Synthesis of (−)-Hennoxazole A

Thomas E. Smith,* Wen-Hsin Kuo, Emily P. Balskus, Victoria D. Bock, Jennifer L. Roizen, Ashleigh B. Theberge, Kathleen A. Carroll, Tomoki Kurihara, and Jeffrey D. Wessler

Department of Chemistry, Williams College, Williamstown, Massachusetts 01267

tsmith@williams.edu

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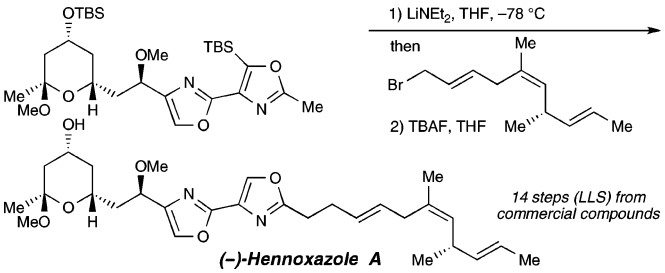

An enantioselective, convergent total synthesis of the antiviral marine natural product (−)-hennoxazole A is completed in 14 steps (longest linear sequence) from commercially available 4-methyloxazole-2-carboxylic acid. Synthesis of the C_1-C_{15} pyran/bisoxazole fragment takes advantage of an aldol-like coupling between a dimethyl acetal and an *N*-acetylthiazolidinethione for the direct, stereoselective installation of the C_8-methoxy-bearing stereocenter. A one-pot acetoacetate acylation/decarboxylation/cyclodehydration of another elaborate thiazolidinethione allows for rapid assembly of the pyran-based ring system. Synthesis of the $C_{15}-C_{25}$ skipped triene side chain fragment makes use of a [2,3]-Wittig−Still rearrangement for efficient installation of the trisubstituted *Z*-double bond. Key late-stage coupling of the two fragments is effected by deprotonation of the methyl group on the bisoxazole system using lithium diethylamide, followed by alkylation with an allylic bromide side chain segment to form the $C_{15}-C_{16}$ bond.

Introduction

In 1991, a research team led by Paul Scheuer at the University of Hawaii reported the isolation and structural elucidation of hennoxazoles A−D (Figure 1) from a species of *Polyfibrospongia* sponge off the coast of Miyako island in Okinawa, Japan.[1] Further investigation by Higa[2] disclosed four additional members of this natural product family, hennoxazoles E−G and hennoxazole A acetate. The most abundant member of the group, hennoxazole A, is also the most active, displaying antiviral activity against herpes simplex 1 ($IC_{50} = 0.6\ \mu g/mL$) and peripheral analgesic activity comparable to that of indomethacin.

Structurally, the hennoxazoles contain a bisoxazole ring system at their molecular core. The muscorides[3] and diazonamides[4] are the only other natural products known to include two contiguous 2,4-disubstituted oxazoles in their frameworks.[5] Other structurally distinctive features of the hennoxazoles include the functionalized pyranyl ring and the nonconjugated triene side chain containing a trisubstituted *Z*-double bond and a remote stereogenic center. The original structure determination work established the correct atomic connectivity but left many of the stereochemical details ambiguous; although the assignment of relative stereochemistry about the C_2-C_6 pyran ring

(1) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173−3174.

(2) Higa, T.; Tanaka, J.-i.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227−2230.

(3) For a lead reference on the muscorides see: Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411−1414.

(4) For a lead reference on the diazonamides see: Poriel, C.; Lachia, M.; Wilson, C.; Davies, J. R.; Moody, C. J. *J. Org. Chem.* **2007**, *72*, 2978−2987.

(5) Several other natural products containing more than two contiguous oxazoles are also known, including the mycalolides, ulapualides, and kabiramides—which have three directly linked oxazole rings—and telomestatin, which has seven. For a review of the syntheses of oxazole-containing natural products, see: (a) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995−12042. (b) Palmer, D., Ed. *Heterocyclic Compounds*; J. Wiley and Sons: New York, 2003; Vol. 60, Part A. (c) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907−1922. For a lead reference on telomestatin, see: (d) Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165−4167.

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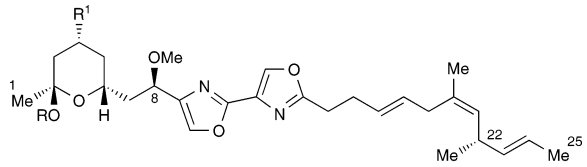
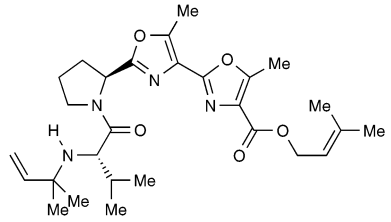
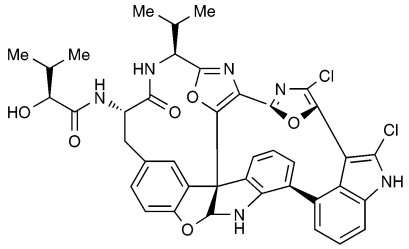


Hennoxazole	R	R^1	
A	Me	OH	(**1a**)
B	Et	OH	(**1b**)
C	Bu	OH	(**1c**)
D	Me	H	(**1d**)
E	H	OH	(**1e**)



Muscoride A
(**2**)



Diazonamide A
(**3**)

FIGURE 1. Bisoxazole natural products.

was secure, the relative stereochemistry of the distant C_8 and C_{22} stereogenic centers and the absolute configuration remained unknown. Pioneering synthetic work by Wipf led to the total synthesis of the unnatural antipode of hennoxazole A and solved the stereochemical puzzle.[6] Key to the Wipf synthesis was a late-stage oxazole ring assembly that involved fragment coupling by amide formation followed by cyclodehydration. The *Z*-geometry of the trisubstituted alkene in the side chain was established through a vinylstannane reagent that was stereoselectively prepared early on. This landmark synthesis proceeded in a 28-step longest linear sequence (LLS) from mercaptoimidazole. Also discovered in the course of this synthesis was the important fact that hennoxazole A and its C_{22} epimer are chromatographically and spectroscopically indistinguishable—except by optical rotation. The consequences of this detail were significant in that any other planned syntheses would require the installation of C_{22} with perfect stereochemical fidelity, since separation would not be possible at the end of the synthesis. Wipf's work also suggested that the skipped triene side chain adopts an interesting helical conformation, principally by virtue of $A^{1,3}$ strain imparted by the trisubstitued *Z*-double bond, and that this structural feature may contribute to the biological activity of hennoxazole A. This conformational predisposition may also have synthetic ramifications that help to mollify concerns about the stability of the nonconjugated triene side chain.

(6) (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157−167.

The same nonbonding interactions that lead to a helical secondary structure in this portion of the molecule may serve to inhibit undesirable isomerization of the side chain double bonds.

Since Wipf's ground-breaking synthesis, two other total syntheses of hennoxazole A, as well as a number of synthetic studies, have been reported.[7] The second total synthesis, by Williams and co-workers, took advantage of a directed allylborane addition to an aldehyde to form the C_7-C_8 bond in the key fragment coupling step.[8] The trisubstituted *Z*-olefin stereochemistry was secured via *syn*-elimination of a 1,2-diol derivative. Also notable is the fact that the bisoxazole unit was fabricated early in the route and carried through the entire sequence. The Williams synthesis proceeded in a 20-step LLS from sodium γ-hydroxybutyrate. The third total synthesis, by Shioiri and co-workers, shared Wipf's strategy for late-stage oxazole formation as the key coupling step.[9] The stereochemistry of the trisubstituted olefin was secured by a *Z*-selective Still−Horner−Wadsworth−Emmons reaction. This synthesis was accomplished in a 25-step LLS from (*R*)-glycidyl tosylate. Herein, we detail our own investigations which have culminated in a 14-step LLS total synthesis of (−)-hennoxazole A.[10]

Results and Discussion

Retrosynthetic Analysis. The development of relatively mild conditions[11] for the preparation of oxazoles has made the late-stage assembly of these ring systems a common, albeit not always efficient, strategy in the synthesis of oxazole-containing targets. Approaches involving end game functionalization of *intact* oxazole rings, however, provide the opportunity to use relatively simple oxazoles as starting materials and then carry these practically inert heterocycles through a variety of synthetic transformations unscathed.[12] In consideration of these issues, our synthetic plan for hennoxazole A (Scheme 1) diverges from precedent and involves late-stage construction of the $C_{15}-C_{16}$ bond by deprotonation of an elaborate bisoxazole fragment (**4**) at the C_{15}-methyl group, followed by alkylation with an allylic bromide side chain fragment (**5**). Further disconnection leads back to achiral bisoxazole dimethyl acetal **6** as a precursor to the direct stereoselective installation of the C_8-methoxy substituent. Likewise, allylic alcohol **7** could be used as the progenitor of the isolated C_{22} stereocenter.

(7) For other synthetic studies see: (a) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415−416. (b) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177−180. (c) Chen, Y. K.; Walsh, P. *J. Am. Chem. Soc.* **2004**, *126*, 3702−3703. (d) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971−1974. (e) Zylstra, E. J.; She, M. W.-L.; Salamant, W. A.; Leahy, J. W. *Synlett* **2007**, 623−627.

(8) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925.

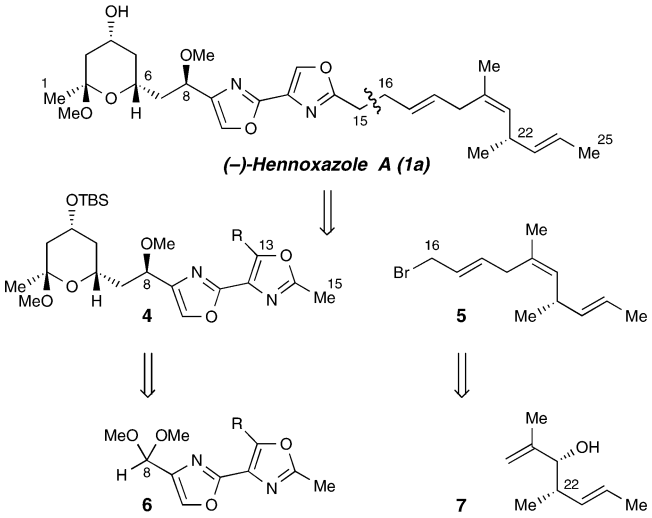
(9) (a) Cheng, Z. Z.; Hamada, Y.; Shioiri, T. *Synlett* **1997**, 109−110. (b) Shioiri, T.; McFarlane, N.; Hamada, Y. *Heterocycles* **1998**, *47*, 73−76. (c) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169−4172. (d) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *57*, 6311−6327.

(10) Portions of this work have been reported in previous papers: (a) Smith, T. E.; Balskus, E. P. *Heterocycles* **2002**, *57*, 1219−1225. (b) Smith, T. E.; Kuo, W.-S.; Bock, V. D.; Roizen, J. L.; Balskus, E. P.; Theberge, A. B. *Org. Lett.* **2007**, *9*, 1153−1155.

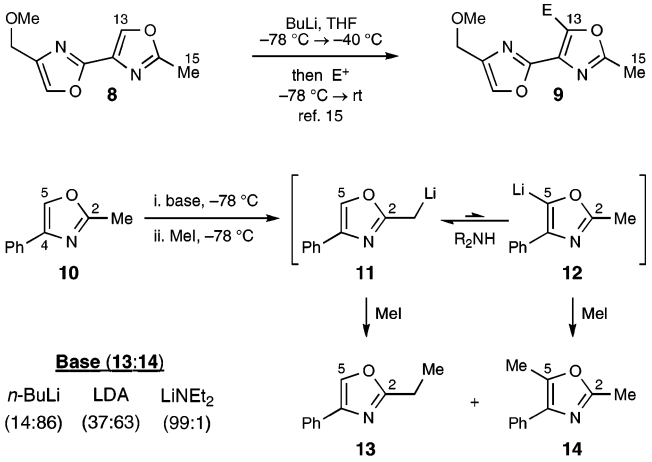
(11) (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168. (b) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331−334. (c) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971−1974. (d) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593−3595.

(12) For a review of the uses of oxazoles as protected carboxylate equivalents see: (a) Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845−856. See also: (b) Evans, D. A.; Nagorny, P.; Xu, R. *Org. Lett.* **2006**, *8*, 5669−5671.

SCHEME 1. Synthetic Strategy toward Hennoxazole A

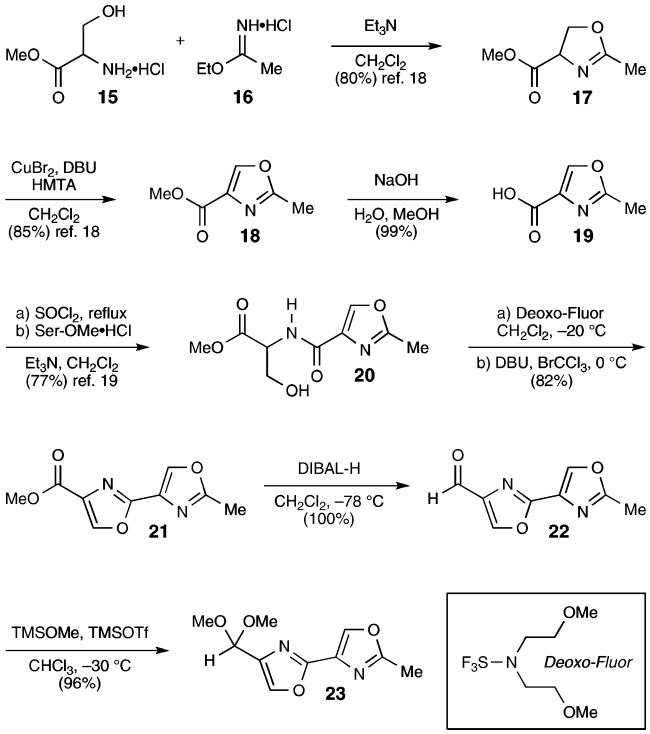


SCHEME 2. Oxazole and Bisoxazole Alkylation Background



Oxazole Alkylation Studies. Synthetically useful lateral metalations of some 2-methyloxazole and thiazole systems have been reported.[13] If these rings are unsubstituted at C_5 (C_{13}, hennoxazole numbering), competitive deprotonation of the C_5-ring hydrogen is frequently observed (Scheme 2).[14] In fact, Williams established that bisoxazole **8** is lithiated exclusively at the C_{13}-position with *n*-BuLi,[15] suggesting that alkylation of **4** at C_{15} might be problematic when R = H. Despite this result, previous work in confronting a similar problem during the synthesis of phorboxazole demonstrated that the regioselectivity of some oxazole deprotonations can be inverted by the choice of base.[16] For example, deprotonation of 2-methyl-4-phenyloxazole (**10**) using *n*-BuLi at −78 °C followed by alkylation with methyl iodide gives a 14:86 ratio of products (**13**:**14**) favoring ring methylation, while the use of $LiNEt_2$ leads to alkylation solely at the C_2-methyl site. This reversal of regioselectivity is thought to arise from the ability of diethylamine to mediate the low-temperature equilibration of a kinetic mixture of otherwise noninterconverting lithiated intermediates (**11** and **12**).[17] Given these results, we thought it possible that the undesired C_{13}-alkylation observed by Williams might be a consequence of kinetic (ring) deprotonation and that we might achieve the desired C_{15}-alkylation on a bisoxazole system such as **6** by equilibrating to the thermodynamic (methyl) lithiated intermediate.

SCHEME 3. Preparation of the Bisoxazole Core



To test the viability of our key side chain coupling strategy, we set out to prepare bisoxazole **23** as a model substrate (Scheme 3). Commercially available (±)-serine methyl ester hydrochloride (**15**) was condensed with ethyl acetimidate (**16**) to give oxazoline **17**, which was oxidized to oxazole **18** as described in Leahy's synthesis of rhizoxin D.[18] Next, following Pattenden's preparation,[19] methyl ester **18** was saponified to carboxylic acid **19**, which was activated as its acid chloride and combined with another equivalent of serine methyl ester to give amide **20**. It is interesting to note that both ester **18** and acid **19** are now commercially available. The one-pot cyclodehydration/

(13) Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410−1413. (b) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058−3063. (c) Vedejs, E.; Zajac, M. A. *Org. Lett*. **2001**, *3*, 2451−2454. (d) Entwistle, D. A.; Jordan, S. I.; Montgomery, J.; Pattenden, G. *Synthesis* **1998**, 603−612. (e) Garey, D; Ramirez, M.-l.; Gonzales, S.; Wertsching, A.; Tith, S.; Keefe, K.; Pena, M. R. *J. Org. Chem*. **1996**, *61*, 4853−4856.

(14) (a) Knaus, G.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1192−1195. (b) Meyers, A. I; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163−3166. (c) Meyers, A. I.; Walker, D. G. *J. Org. Chem.* **1982**, *47*, 2999−3000. (d) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111−5123. (e) Hamana, H.; Sugasawa, T. *Chem. Lett*. **1983**, 333−336. For a review of oxazole metalation see: (f) Iddon, B. *Heterocycles* **1994**, *37*, 1321−1346.

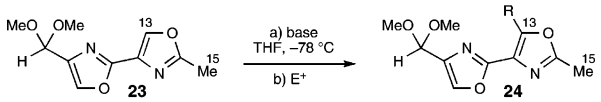
(15) Williams, D. R.; Brooks, D.; Meyer, K. G. *Tetrahedron Lett.* **1998**, *39*, 8023−8026.

(16) For the original solution to this problem see: (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87−90. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533−2536. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. For subsequent applications of this method to the synthesis of phorboxazoles see: (d) González, M. A.; Pattenden G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255−1258. (e) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem. Eur. J.* **2006**, *12*, 1185−1204. (f) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett*. **2006**, *8*, 6039−6042

(17) For further investigation of this effect see: Smith, T. E.; Mourad, M. S.; Velander, A. J. *Heterocycles* **2002**, *57*, 1211−1217.

(18) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234.

SCHEME 4. Bisoxazole Model Alkylations



Base	Electrophile	R	Product	Yield
n-BuLi	MeI	Me	**24a**	78%
LDA	MeI	Me	**24a**	—[a]
$LiNEt_2$	MeI	Me	**24a**	—[a]
n-BuLi	TBSOTf	TBS	**24b**	88%

[a] Only product observed by ^{1}H NMR. No yield calculated.

oxidation method of Wipf and Williams[11a] was then used to generate bisoxazole methyl ester **21** in 82% yield, an improvement over previous multistep preparations.[19,11b] Partial reduction with DIBAL-H gave aldehyde **22** in quantitative yield. Finally, Noyori conditions[20] were used to generate dimethyl acetal **23** in 96% yield.

Consistent with Williams' studies of **8**,[15] treatment of model bisoxazole **23** with *n*-BuLi led to deprotonation exclusively at the C_{13}-ring position (Scheme 4), with no deprotonation occurring at the C_{15}-methyl group. Unfortunately, replacing the base with LDA or $LiNEt_2$ did not alter the regioselectivity, suggesting that, in the case of **23**, deprotonation at C_{13} is thermodynamically as well as kinetically favored.[21] Attempts to alkylate the dianion of **23** were not fruitful. As an indirect solution to this predicament, we chose to block C_{13} with a silyl protecting group.[22] Although TMS and TES groups were found to be too labile for this purpose, since they underwent silyl transfer processes upon C_{15}-deprotonation, the TBS group proved to be suitable. Treatment of **23** with *n*-BuLi followed by addition of TBSOTf led to C_{13}-protected bisoxazole **24b** in 88% yield.

To model our key coupling step, we treated protected bisoxazole **24b** with several different strong bases and quenched with MeI (Scheme 5). Gratifyingly, alkylation occurred predominantly at the desired C_{15} site to give **25**, with $LiNEt_2$ providing the best results. It is interesting to note that *n*-BuLi and LDA both gave poor conversion and small amounts of product **26**—methylated at *both* the C_{15}-methyl and C_{10}-ring positions—at the expense of starting material conversion.[23] No significant monomethylation at C_{10} was observed. To better mimic the reactivity of the actual side chain fragment (**5**), we also alkylated **24b** with allyl iodide and prenyl bromide, both of which gave excellent results with $LiNEt_2$. Importantly, treatment of the alkylated products (**27** and **29**) with TBAF demonstrated that the oxazole could be cleanly deprotected under mild conditions.

Side Chain Fragment Synthesis. Having established a viable coupling strategy, we set out to prepare the actual skipped triene side chain fragment (**5**). As our starting material, we selected known allylic alcohol **7** (Scheme 6). For our initial studies, we prepared this material according to Williams' published route,[8] which derives from (*S*)-3-pentyn-2-ol (**31**). This compound can be obtained from the C-methylation of commercially available (*S*)-3-butyn-2-ol or by enzymatic resolution of racemic **31**.[24] Interestingly, we discovered some erosion of enantiomeric excess in our synthetic sequence resulting from the [2,3]-Wittig rearrangement.[25] Although there was essentially complete transfer of stereochemical information between methallyl ether **32** and major *syn*-product **7**, it turned out that the same was not true for minor *anti*-product **33**, which was obtained in only 77% ee.[26] Since both diastereomers converge on the same compound (**37**; see Scheme 7), any *ent*-**33** carried forward would be transformed into *ent*-**37**, thus eroding the side chain ee. The importance of side chain enantiomeric purity to the eventual success of the asymmetric synthesis has already been noted. We were able to remove the offending *anti*-diastereomer (**33**) via chromatography on silver nitrate-impregnated silica gel,[27] providing *syn*-diastereomer **7** in 95% ee.

We anticipated that kinetic resolution of racemic **7** using Fu's planar-chiral DMAP catalyst could be used as an alternative asymmetric preparation of this starting material.[28] Similar allylic alcohols have been resolved with selectivity factors in the 10−25 range.[29] In the event, kinetic resolution of *rac*-**7** using acetic anhydride proceeded with good selectivity ($s = 10.4$), but the reaction was too slow to be of practical use. Experiments at higher temperatures or catalyst/reagent loadings were not investigated.

Finally, we investigated the asymmetric pentenylation method of Hoffmann.[30] Allyl boronate **35** was prepared and allowed to react with methacrolein (**36**). This very direct approach provided desired allylic alcohol **7** in 81% yield and 98% ee.

With a supply of enantiopure starting material **7** in hand, we proceeded with our synthesis of side chain **5** (Scheme 7). The trisubstituted C_{20}−C_{21} *Z*-double bond was expeditiously installed via a [2,3]-Wittig−Still rearrangement; avoidance of $A^{1,2}$-strain in the early transition state presents one diastereoface of the C_{19}−C_{20} double bond to the intermediate C_{18}-anion, leading to homoallylic alcohol **37** as a single isomer.[31] Notably, this key transformation accomplishes in one step what had required six steps in Williams' synthesis.[32] Dess−Martin oxidation[33] next gave aldehyde **38**, which was subjected to an *E*-selective Horner−Wadsworth−Emmons olefination to give ester **39**. Reduction with DIBAL-H then provided allylic alcohol **40** in

(19) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2415−2428.

(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

(21) Williams carried out semiempirical calculations also suggesting that the ring-lithiated intermediate was thermodynamically favored due to chelation with the adjacent oxazole nitrogen. See ref 15.

(22) Silylation at C_5 was one approach to solving "the oxazole problem" in virginiamycin: (a) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1983**, *24*, 4391−4392. (b) Fujita, E. *Heterocycles* **1984**, *21*, 41−60.

(23) Product identities and ratios were determined using a combination of ^{1}H NMR and GC−MS analysis.

(24) (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529−1532. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2753.

(25) Tsai, D. J.-S.; Midland, M. M. *J. Am. Chem. Soc.* **1985**, *107*, 3915−3918.

(26) Stereochemical erosion in the *syn*-diastereomer of this type of [2,3]-Wittig rearrangment has been observed previously: Tsubuki, M.; Kamata, T.; Nakatani, M.; Yamazaki, K.; Matsui, T.; Honda, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4725−4736.

(27) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425−447.

(28) For a review see: Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547.

(29) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009−1010.

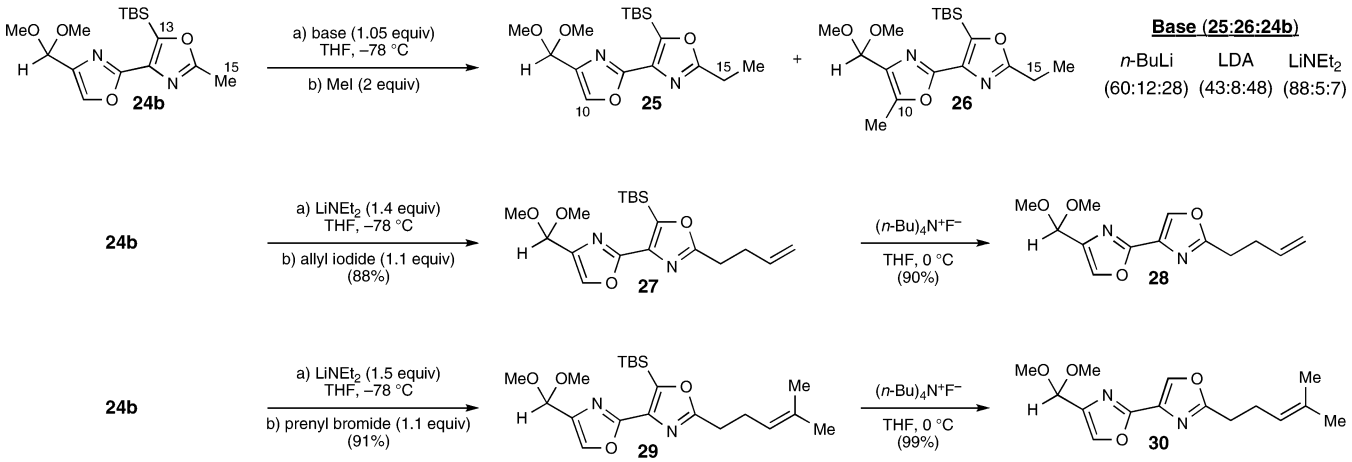
(30) For the original reference, see: (a) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *122*, 1783−1789. For an improved preparation of the (*Z*)-pentenyl boronate reagent, see: (b) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388−2390.

(31) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928. (b) Still, W. C.; McDonald, J. H., III; Collum, D. B.; Mitra, A. *Tetrahedron Lett.* **1979**, *20*, 593−594. For a review see: (c) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594−604.

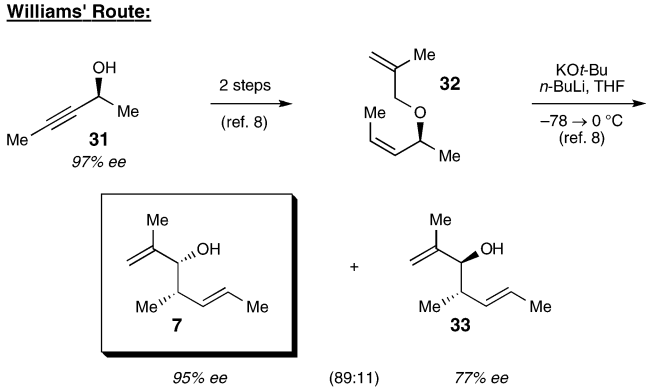
(32) Homoallylic alcohol **37** is also an intermediate in Williams's synthesis, but required six steps to prepare from **7**.

(33) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

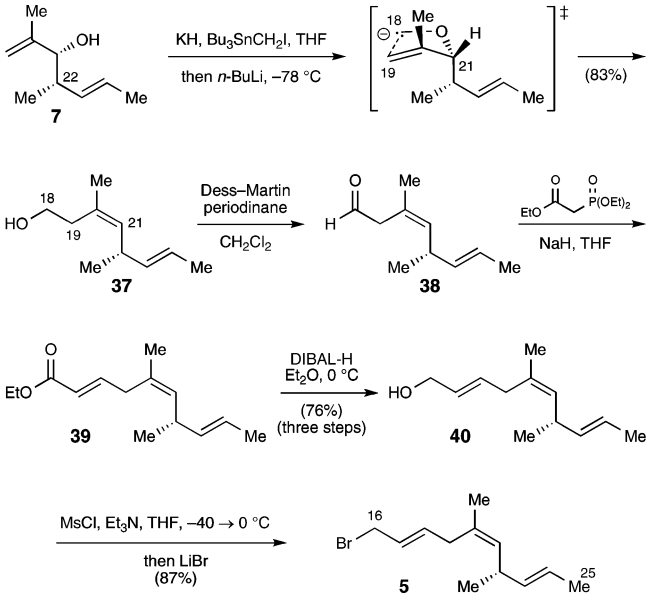
SCHEME 5. Protected Bisoxazole Model Alkylations



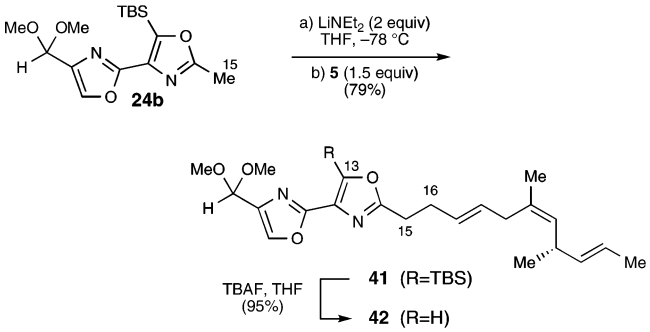
SCHEME 6. Preparation of the Side Chain Precursor (7)



SCHEME 7. Synthesis of the $C_{16}-C_{25}$ Side Chain Fragment (5)



SCHEME 8. Model Fragment Coupling with the Actual Side Chain (5)

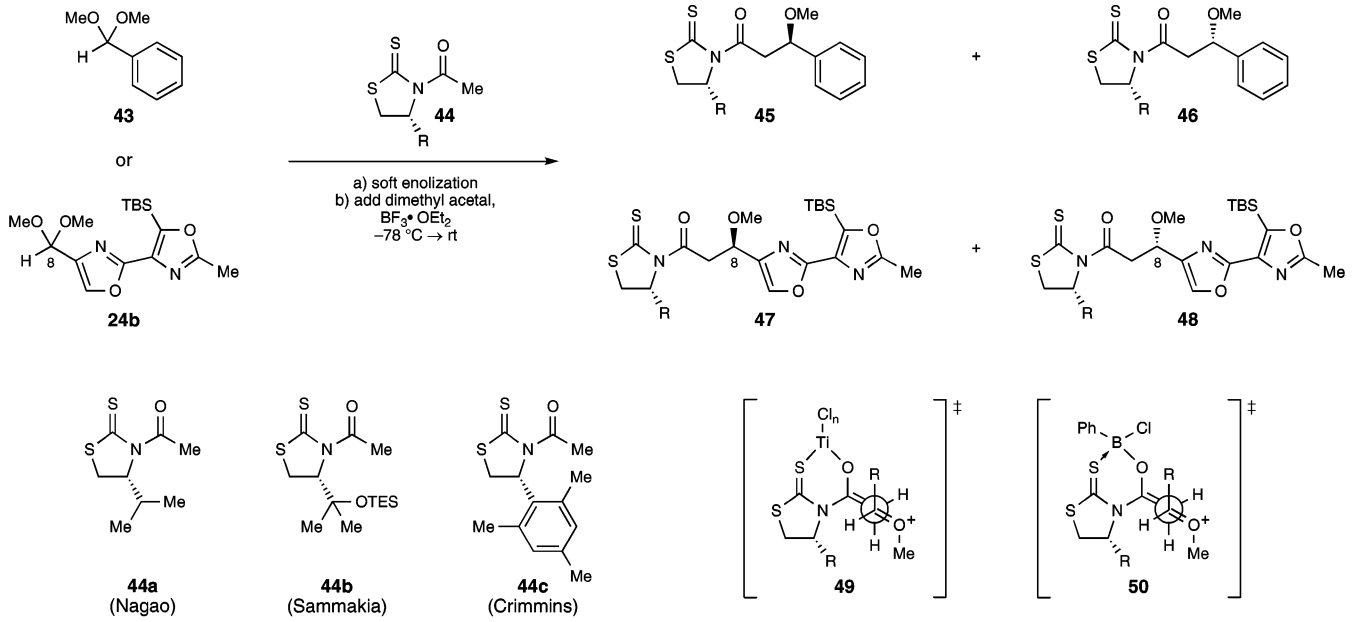


76% yield over the three steps. Treatment with mesyl chloride and lithium bromide completed the synthesis of electrophilic coupling fragment **5**.

Once the actual side chain (**5**) was prepared, a final model coupling was undertaken (Scheme 8). Deprotonation of TBS-protected model bisoxazole **24b** with $LiNEt_2$, as before, and treatment with side chain allylic bromide **5** gave the desired alkylation product (**41**) with no evidence of a competing S_N2' pathway. This comforting result indicated an even greater likelihood that our final fragment coupling event would be successful.

Pyran/Bisoxazole Fragment Synthesis. Encouraged by these experiments, we carried on with our synthesis of pyran/bisoxazole fragment **4**. The first significant challenge in this endeavor involved establishing the desired absolute stereochemical configuration at C_8. It was our hope that dimethyl acetal **24b** could be used to install the C_8-methoxy group *directly*, without requiring the formation of a methyl ether via a multiple-step reaction sequence. The stereoselective aldol-like reactions

SCHEME 9. Condensation Reactions of *N*-Acetylthiazolidinethiones with Dimethyl Acetals



Entry	Auxliary R	Acetal	Enolization Conditions	Products	Diastereomer Ratio	Yield of Purified Major Diastereomer
1	*i*-Pr (**44a**)	Ph (**43**)	$TiCl_4$, Hünig's base	**45a + 46a**	(85:15)	69%
2	*i*-Pr (**44a**)	Ph (**43**)	$PhBCl_2$, sparteine	**45a + 46a**	(71:29)	32%
3	*i*-Pr (**44a**)	Bisoxazole (**24b**)	$TiCl_4$, Hünig's base	**47a + 48a**	(20:80)	67%
4	*i*-Pr (**44a**)	Bisoxazole (**24b**)	$PhBCl_2$, sparteine	**47a + 48a**	(67:33)	59%[a]
5	CMe_2(OTES) (**44b**)	Ph (**43**)	$TiCl_4$, Hünig's base	**45b + 46b**	(82:18)[b]	—[c]
6	CMe_2(OTES) (**44b**)	Ph (**43**)	$PhBCl_2$, sparteine	**45b + 46b**	(84:16)	—[c]
7	CMe_2(OTES) (**44b**)	Bisoxazole (**24b**)	$TiCl_4$, Hünig's base	**47b + 48b**	—[d]	—[c]
8	CMe_2(OTES) (**44b**)	Bisoxazole (**24b**)	$PhBCl_2$, sparteine	**47b + 48b**	(86:14)	53%
9	Mesityl (**44c**)	Ph (**43**)	$TiCl_4$, Hünig's base	**45c + 46c**	(58:42)	—[c]
10	Mesityl (**44c**)	Ph (**43**)	$PhBCl_2$, sparteine	**45c + 46c**	(34:66)	—[c]

[a] Combined yield of both diastereomers. [b] Reaction only proceeded to 50% conversion. [c] No yield calculated. [d] Acetal was consumed, but **47b** and **48b** not observed.

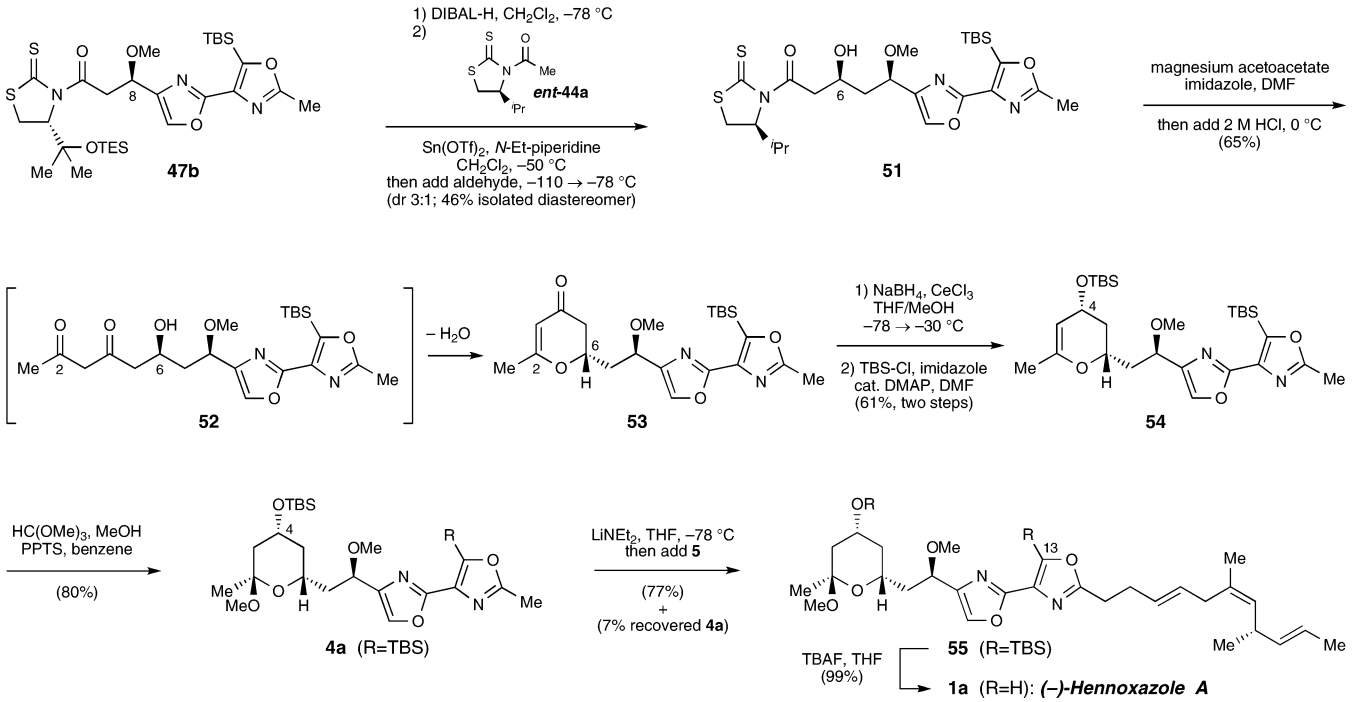
between *N*-acylthiazolidinethiones and acetals reported by Urpí provided inspiration toward this end.[34]

Several chiral auxiliaries and soft enolization conditions were surveyed to find suitable reaction conditions (Scheme 9). Urpí's original conditions were explored first (entry 1). Treatment of the titanium enolate of *i*-Pr-substituted thiazolidinethione **44a** with benzaldehyde dimethyl acetal (**43**) in the presence of the Lewis acid, BF_3·OEt_2, gave *anti*-isomer **45a** and *syn*-isomer **46a** in an 85:15 ratio in accordance with Urpí's reported results. The diastereoselectivity for this reaction can be rationalized by an open transition state, such as **49**, that allows for an *anti*-approach of the enolate to the activated carbonyl and minimizes interaction between the bulky R and thione substituents. Interestingly, when these same conditions were used with bisoxazole dimethyl acetal **24b** (entry 3), the opposite diastereomer was obtained preferentially. We posit that this reversal in selectivity may be due to the ability of an oxazole nitrogen atom to coordinate with the titanium center and alter the organization of the transition state. Regardless of the rationale, the two diastereomers were produced in a 20:80 ratio—certainly acceptable if we were to use the opposite enantiomer of the thione auxiliary. Unfortunately, the two products (**47a** and **48a**) were very difficult to separate, which limited the practical application of this method to our synthesis. As a consequence, we probed additional reaction conditions.

Intrigued by Sammakia's recent reports of boron-mediated aldol reactions of *N*-acetylyhiazolidinethiones,[35] we decided to evaluate whether these conditions might be suitable for reactions with acetals. In the simplest case (entry 2) this seemed to be borne out, although the diastereomer ratio and isolated yield were suboptimal. Importantly, the bisoxazole substrate (entry

(34) Cosp, A.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4629−4631.

SCHEME 10. Synthesis of the C_1−C_{15} Pyran/Bisoxazole Fragment (4a) and Completion of the Total Synthesis



4) gave the same sense of asymmetric induction as the simple benzaldehyde dimethyl acetal. A transition-state model for this boron-mediated transformation (**50**) is similar to that of the titanium-promoted case (**49**), but differs critically in the facility of the titanium center to coordinate with additional ligands. Since Sammakia demonstrated much higher levels of diastereoselection when he substituted a *t*-Bu substituent (or the pseudo-*t*-Bu group in the form of a $-CMe_2$(OTES) group) for the *i*-Pr substituent on the chiral auxiliary, we explored those changes as well using **44b** (entries 6 and 8). Greater diastereoselectivity was indeed observed. Under these conditions, the desired major isomer **47b** was obtained in 53% isolated yield, and although this yield was somewhat lower than could be obtained for **47a**, the products were easier to separate.[36] About 10% β-eliminated product was also obtained under these conditions. The higher susceptibility of the $-CMe_2$(OTES)-substituted auxiliaries toward hydrolysis on silica gel may also be reflected in the somewhat diminished isolated yields obtained after chromatography. Additionally, a more conventional two-step approach involving an auxiliary-directed aldol reaction followed by methyl ether formation was thwarted by β-elimination difficulties. Overall, this direct pathway (entry 8) appeared to be the best compromise of increased structural complexity and yield and was appropriated to advance material to the forefront of the synthesis.

In further model studies, the titanium enolization conditions did not appear to be entirely compatible with the $-CMe_2$-(OTES)-substituted systems. Poor conversion was observed with benzaldehyde dimethyl acetal (entry 5), and no desired product was obtained with the bisoxazole acetal (entry 7). It was also demonstrated that the mesityl-substituted auxiliaries (such as **44c**), very recently disclosed by Crimmins,[37] do not provide useful levels of diastereoselectivity for these types of condensation reactions (entries 9 and 10).

Pressing on with our synthesis (Scheme 10), the thione auxiliary was reductively cleaved from **47b** using DIBAL-H.[38] The resulting β-methoxy aldehyde was prone to β-elimination and thus was immediately subjected to an auxiliary-directed acetate aldol reaction using *ent*-**44a**. Reagent-based stereochemical control was required to set the desired 1,3-*syn*-relationship between the C_6 and C_8 oxygen substituents, effectively overriding the 1,3-*anti*-selectivity bias intrinsic to such β-methoxy aldehyde substrates.[39] We eventually settled on the original tin enolate conditions of Nagao for this transformation to give aldol adduct **51**.[40] Use of Sammakia's auxiliary (**44b**) and boron enolate gave a lower selectivity (67:34) and isolated yield (43% yield of an inseparable mixture of product diastereomers). We expect that Crimmins' mesityl auxiliary (*ent*-**44c**) and titanium enolate would be best suited here, but have not evaluated this prospect.

Encouraged by our previous success with the kavalactones in efficiently refunctionalizing *N*-acylthiazolidinethiones,[41] we postulated that this similar aldol product (**51**) might be directly converted into methyl ketone **52**. Gratifyingly, treatment with magnesium acetoacetate[42] and imidazole not only led to the desired transacylation reaction—presumably through the intermediacy of an acyl imidazolide—but also, upon quenching with

(35) (a) Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23−25. (b) Zhang, Y.; Sammakia, T. *Org. Lett.* **2004**, *6*, 3139−3141. (c) Zhang, Y.; Sammakia, T. *J. Org. Chem.* **2006**, *71*, 6262−6265.

(36) As an additional benefit, product **47b** could be reduced to the corresponding aldehyde in a single step using DIBAL-H, whereas attempted reduction of **47a** and **48a** always gave significant amounts of overreduction to the primary alcohols, which would necessitate a two-step reduction/oxidation sequence.

(37) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149−152.

(38) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902. (b) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191−2194.

(39) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(40) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393.

(41) Smith, T. E.; Djang, M.; Velander, A. J.; Downey, C. W.; Carroll, K. A.; van Alphen, S. *Org. Lett.* **2004**, *6*, 2317−2320.

aqueous acid, provided cyclodehydrated pyrone **53**. Notably, this transformation is accomplished in a single step without the need for protecting groups and made early approaches involving elaboration of a C_2-C_6 δ-lactone obsolete. Luche reduction[43] gave an unstable allylic alcohol, which was immediately protected as its TBS ether (**54**) in a combined yield of 61%. Mixed methyl acetal formation, in accordance with Wipf's pioneering work,[6] finalized the synthesis of C_1-C_{15} pyran/bisoxazole coupling fragment **4a**.

With both coupling partners in hand, we endeavored to unite them in the pivotal transformation of the synthesis. Using the same conditions that had been successful for model fragment couplings, treatment of bisoxazole **4a** with $LiNEt_2$ and allylic bromide **5** led to the anticipated union in 77% yield along with 7% unalkylated **4a**, thus securing the entire carbon framework of the natural product. Double TBS deprotection of **55** provided (−)-hennoxazole A, having spectra identical to those published previously.[6,8,9]

Conclusions

We have developed a convergent asymmetric route to hennoxazole A that proceeds in a longest linear sequence of 17 steps from serine methyl ester and only 14 steps from commercially available 4-methyloxazole-2-carboxylic acid (**19**). Contributing to the efficiency of this synthesis is the direct use of a dimethyl acetal for the stereocontrolled installation of the C_8-methyl ether in a single step. The rapid functionalization of the thiazolidinethione-derived aldol adducts and the necessity of only two (TBS) protecting groups—which are both removed in the final step—also convey significant step economy. Finally, the key fragment coupling, featuring the alkylation of an intact bisoxazole core, renders this synthesis highly convergent.

Experimental Section

Preparation of Allylic Alcohol 7.[30] To a solution of pentenyl boronate **35** (124.7 mg, 0.410 mmol, 1 equiv) in hexanes (0.82 mL) at 0 °C was added methacrolein (68 μL, 0.82 mmol, 2 equiv). The flask was capped, sealed with Teflon tape, and stirred in a 4 °C cold room for 36 h. The solution was warmed to rt, and the hexanes were removed in vacuo (≥50 mmHg). The residue was dissolved in THF (1.92 mL), 3 M NaOH (0.48 mL) and 30% aq H_2O_2 (0.38 mL) were added sequentially, and the mixture was heated to reflux (bath temp 80 °C) for 2 h. The mixture was cooled to rt and was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo (≥50 mmHg). The product was purified via automated silica column chromatography (0 → 20% Et_2O/pentane over 20 min, 10 g column; TLC R_f = 0.30, 20% Et_2O/hexanes, anisaldehyde stain) to provide allylic alcohol **7** (46.3 mg, 81%) as a clear, colorless oil. Chiral GC (Chiraldex G-TA column, 30 m × 0.25 mm, 30 psi of He, 50 °C, 1 °C/min ramp) indicated the ee to be 98% (t_{major} = 24.38 min, t_{minor} = 25.62 min). Other data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (dq, J = 15.4, 6.4 Hz, 1H), 5.40 (ddq, J = 15.3, 7.1, 1.2 Hz, 1H), 4.95 (s, 1H), 4.88 (s, 1H), 3.90 (dd, J = 4.5, 4.4 Hz, 1H), 2.36 (dq, J = 12.8, 6.7 Hz, 1H), 1.71 (s, 3H), 1.68 (d, J = 6.2 Hz, 3H), 1.56 (d, J = 3.7 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 133.6, 125.3, 111.6, 78.8, 39.7, 18.6, 18.1, 14.2 ppm; IR (film) 3403, 2970, 2920, 2877, 1652, 1452, 1376, 1295, 1115, 1023, 981, 898, 557 cm^{-1}; $[\alpha]_D^{24}$ = +5.4° (c = 1.01, $CHCl_3$); HRMS (EI) exact mass calcd for $C_9H_{16}O$ $[M]^+$ 140.1201, found 140.1192.

Preparation of Trisubstituted Alkene 37.[32] To a 10 mL concentration flask was added KH (290 mg of a 35% dispersion in mineral oil, 2.38 mmol, 2.2 equiv). The white solid was washed in dry pentanes (3 × 5 mL) and suspended in dry THF (2 mL) at 0 °C. To this suspension was added allylic alcohol **7** (152 mg, 1.08 mmol, 1 equiv) via cannula in THF (1.2 mL), producing a cloudy yellow solution. Dibenzo-18-crown-6 (catalytic amount) was added as a white powder, followed by addition of Bu_3SnCH_2I[44] (560 mg, 1.30 mmol, 1.2 equiv) via cannula in THF (0.8 mL). The solution became a light brown color and was warmed to rt. After 2 h, the solution was cooled to −78 °C. *n*-Butyllithium (1.1 mL of a 1.56 M in hexanes, 1.63 mmol, 1.5 equiv) was added dropwise via syringe down the cold wall of the flask, forming an orange solution. The solution was stirred at −78 °C for 2 h. The orange color gradually changed to light brown and then became more yellow. The reaction mixture was partitioned between Et_2O (10 mL) and satd aq NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a clear, yellow oil and a red-brown precipitate. The product was purified via automated silica column chromatography (0 → 15% EtOAc/hexanes over 30 min, 110 g column; TLC R_f = 0.42, 15% EtOAc/hexanes, anisaldehyde stain) to provide homoallylic alcohol **37** (138 mg, 83% yield) as a clear, colorless oil. Due to the volatility of alcohol **37**, it should not be exposed to pressures lower than 5 mmHg. Chiral GC (Chiraldex G-TA column, 30 m × 0.25 mm, 30 psi of He, 50 °C, 0.6 °C/min ramp) gave only 85% resolution of the two enantiomer peaks but was consistent with a product ee identical to that of the starting material (t_{major} = 45.37 min, t_{minor} = 45.99 min). Other data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45−5.34 (m, 2H), 5.18 (d, J = 9.6 Hz, 1H), 3.72−3.62 (m, 2H), 3.12−3.03 (m, 1H), 2.37 (dt, J = 13.4, 6.4 Hz, 1H), 2.30 (dt, J = 13.4, 6.4 Hz, 1H), 1.72 (d, J = 1.2 Hz, 3H), 1.64 (d, J = 4.7 Hz, 3H), 1.34 (br s, 1H), 1.01 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 133.2, 129.7, 122.8, 60.7, 35.4, 35.3, 23.5, 21.7, 17.9 ppm; IR (film) 3325, 2963, 2870, 1449, 1377, 1042, 968, 868 cm^{-1}; $[\alpha]_D^{24}$ = −59.3° (c = 1.00, $CHCl_3$); HRMS (EI) exact mass calcd for $C_{10}H_{18}O$ $[M]^+$ 154.1358, found 154.1358.

Preparation of Thiazolidinethione Methyl Ether 47b. To a 100 mL flask was added (*R*)-*N*-acetyl-4-[CMe_2(OTES)]-thiazolidinethione (**44b**) (103.1 mg, 0.309 mmol, 2 equiv) in CH_2Cl_2 (1.5 mL). After being flushed with Ar, the stirring solution was cooled to 0 °C, and $PhBCl_2$ (0.041 mL, 0.309 mmol, 2 equiv) was added dropwise via syringe. After 10 min, sparteine (0.142 mL, 0.618 mmol, 4 equiv) was added via syringe. The resulting solution was warmed to rt and stirred for 30 min. The solution was cooled to −78 °C, and bisoxazole dimethyl acetal **24b** (52.7 mg, 0.155 mmol, 1 equiv) was added dropwise via cannula in CH_2Cl_2 (0.5 mL) followed by the dropwise addition of BF_3·OEt_2 (0.030 mL, 0.232 mmol, 1.5 equiv). The solution was stirred at −78 °C for 1.5 h and then was warmed to rt over 2 h. After being stirred at rt for 1 h, the reaction was quenched with satd aq NH_4Cl (5 mL). The contents of the flask were transferred to a separatory funnel containing a 4:1 mixture of hexanes/CH_2Cl_2 (80 mL). The layers were separated, the aqueous layer was re-extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. ^{1}H NMR integration of the unpurified product indicated an 86:14 diastereomer ratio. This material was purified via automated silica column chromatography (0.7% → 3.5% acetone/CH_2Cl_2, 110 g column; TLC R_f = 0.40 in 2% acetone/CH_2Cl_2) to provide diastereomerically pure methyl ether **47b** (53 mg, 53% yield) as a clear, yellow oil. In

(42) (a) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed.* **1979**, *18*, 72. (b) Ohta, S.; Tsujimura, A.; Okamoto, M. *Chem. Pharm. Bull.* **1981**, *29*, 2762−2768.

(43) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848−5849.

(44) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151−166. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487.

much larger reactions where **24b** was used in 0.712 and 1.807 g amounts, the isolated yields were 48% and 46%, respectively. Other data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.28 (d, J = 8.2 Hz 1H), 4.84 (dd, J = 7.5, 5.1 Hz, 1H), 4.02 (dd, J = 17.8, 7.6 Hz, 1H), 3.76 (dd, J = 17.8, 5.2 Hz, 1H), 3.46 (dd, J = 11.3, 8.1 Hz, 1H), 3.39 (d, J = 11.4 Hz, 1H), 3.36 (s, 3H), 2.53 (s, 3H), 1.30 (s, 6H), 0.95 (t, J = 7.5 Hz, 9H), 0.95 (s, 9H), 0.62 (q, J = 7.8 Hz, 6H), 0.381 (s, 3H), 0.377 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 170.5, 165.0, 156.6, 154.9, 141.1, 139.0, 135.4, 76.7, 72.5, 72.4, 57.0, 43.4, 29.9, 28.1, 26.5, 26.1, 17.6, 13.8, 7.0, 6.6, −5.9 ppm; IR (film) 2954, 2929, 2876, 1699, 1612, 1586, 1464, 1367, 1317, 1250, 1154 cm^{-1}; $[\alpha]_D^{25}$ = −93.3° (c = 1.02, $CHCl_3$); HRMS (CI) exact mass calcd for $C_{29}H_{50}N_3O_5S_2Si_2$ [M + H]$^+$ 640.2730, found 640.2745.

Preparation of Pyranone 53. To a 10 mL flask containing alcohol **51** (238.0 mg, 0.431 mmol, 1 equiv) in DMF (2.7 mL) under an Ar atmosphere was added magnesium acetoacetate (195 mg, 0.861 mmol, 2 equiv) and imidazole (32.2 mg, 0.474 mmol, 1.1 equiv). After being stirred for 29 h, the mixture was cooled to 0 °C in an ice bath, diluted with THF (3 mL), quenched with 7.5 mL of 2 M HCl, and stirred overnight. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This material was purified via automated silica column chromatography (55% → 80% EtOAc/hexanes, 110 g column; TLC R_f = 0.40 in 80% EtOAc/hexanes) to provide dihydropyranone **53** (121.5 mg, 65% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.30 (s, 1H), 4.51−4.43 (m, 2H), 3.33 (s, 3H), 2.55 (s, 3H), 2.58−2.40 (m, 3H), 2.25 (ddd, J = 13.5, 6.0, 6.0 Hz, 1H), 1.97 (s, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 174.0, 165.1, 156.8, 154.8, 141.1, 138.8, 135.4, 104.8, 76.2, 72.6, 56.6, 40.6, 39.1, 26.3, 20.9, 17.5, 13.7, −6.00 ppm; IR (film) 2954, 2929, 2859, 1670, 1612, 1465, 1399, 1334, 1249, 1109, 1033, 842, 824, 781, 680 cm^{-1}; $[\alpha]_D^{25}$ = −36.7° (c = 0.96, $CHCl_3$); HRMS (CI) exact mass calcd for $C_{22}H_{33}N_2O_5Si$ [M + H]$^+$ 433.2159, found 433.2171.

Preparation of Bis-TBS-Protected Hennoxazole A (55). A 0.5 M solution of $LiNEt_2$ was prepared by addition of *n*-BuLi (1.00 mL of a 2.72 M solution in hexanes, 2.72 mmol) to a 25 mL concentration flask containing diethylamine (0.310 mL, 3.00 mmol) in THF (4.13 mL) at −78 °C under an atmosphere of argon. After 5 min, the flask was warmed to 0 °C. Mixed methyl acetal **4a** (R = TBS) (69.0 mg, 0.119 mmol, 1 equiv) in a 10 mL concentration flask was diluted with THF (2.0 mL). The solution was cooled to −78 °C under an atmosphere of argon, and the $LiNEt_2$ prepared above was added dropwise until a yellow color persisted (to remove any adventitious acid source—about 4 drops). After this zero point, $LiNEt_2$ (0.285 mL of a 0.5 M solution in THF, 0.143 mmol, 1.2 equiv) was added dropwise via a gastight syringe. The reaction took on a bright orange-red color. After the reaction mixture was stirred at −78 °C for 15 min, allylic bromide **5** (31.8 mg, 0.131 mmol, 1.1 equiv) was added dropwise via cannula in THF (1.65 mL), causing the reaction to become progressively lighter orange-yellow. After 15 min, the reaction was quenched with satd aq $NaHCO_3$ (5 mL), diluted with EtOAc (5 mL) and warmed to rt. The layers were separated, and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This material was purified via automated silica column chromatography (0 → 20% EtOAc/hexanes, TLC R_f = 0.62 in 30% EtOAc/hexanes) to provide protected hennoxazole **55** (67.7 mg, 77% yield) as a clear colorless oil along with unreacted starting material **4a** (4.6 mg, 7%) and doubly alkylated product (6.1 mg, 6%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 5.51−5.38 (m, 2H), 5.38−5.31 (m, 2H), 4.99 (d, J = 9.2 Hz, 1H), 4.45 (dd, J = 8.1, 6.0 Hz, 1H), 3.97 (dddd, J = 10.8, 10.8, 4.7, 4.7 Hz, 1H), 3.49−3.42 (m, 1H), 3.28 (s, 3H), 3.04−2.95 (m, 1H), 3.00 (s, 3H), 2.92 (t, J = 7.6 Hz, 2H), 2.71 (dd, J = 14.3, 6.1 Hz, 1H), 2.66 (dd, J = 14.3, 6.1 Hz, 1H), 2.51 (dt, J = 7.2, 6.7 Hz, 2H), 2.18−2.07 (m, 2H), 1.95 (ddd, 1H, J = 12.8, 4.7, 1.5 Hz), 1.97 (ddt, J = 12.3, 4.7, 2.4 Hz, 1H), 1.63 (d, J = 4.0 Hz, 3H), 1.60 (d, J = 1.4 Hz, 3H), 1.34 (dd, J = 12.6, 11.1 Hz, 1H), 1.28 (s, 3H), 1.22 (ddd, J = 11.8, 11.8, 11.8 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.95 (s, 9H), 0.86 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 156.6, 154.7, 141.3, 139.0, 136.1, 136.0, 132.0, 130.4, 129.5, 128.7, 122.5, 99.6, 72.7, 65.7, 65.1, 56.3, 47.6, 45.3, 41.0, 40.3, 35.3, 35.2, 30.0, 28.2, 26.5, 25.8, 23.7, 23.3, 21.4, 18.0, 17.9, 17.6, −4.6, −5.9 ppm; IR (film) 2929, 2857, 1612, 1463, 1376, 1252, 1192, 1086, 969, 838, 778, 621, 525, 506, 489 cm^{-1}; $[\alpha]_D^{25}$ = −40.3° (c = 1.01, $CHCl_3$); HRMS (CI) exact mass calcd for $C_{41}H_{70}N_2O_6Si_2Li$ [M + Li]$^+$ 749.4933, found 749.4917.

Preparation of (−)-Hennoxazole A (1a). To a 25 mL flask containing protected hennoxazole **55** (67.7 mg, 0.091 mmol, 1 equiv) in THF (6.0 mL) under Ar(g) was added TBAF (547 μL of a 1.0 M solution in THF, 0.547 mmol, 6 equiv). The solution was stirred for 24 h, after which the reaction was concentrated in vacuo and purified via flash chromatography (0 → 100% EtOAc, TLC R_f = 0.27 in 80% EtOAc/hexanes) to provide **1a** (46.2 mg, 99% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.63 (s, 1H), 5.50−5.38 (m, 2H), 5.37−5.31 (m, 2H), 4.99 (d, 1H, J = 9.2 Hz, 1H), 4.45 (t, J = 7.1 Hz, 1H), 4.04 (dddd, J = 10.8, 10.8, 4.5, 4.5 Hz, 1H), 3.61−3.54 (m, 1H), 3.31 (s, 3H), 3.07 (s, 3H), 3.03−2.95 (m, 1H), 2.90 (t, J = 7.6 Hz, 2H), 2.71 (dd, J = 14.4, 6.5 Hz, 1H), 2.66 (dd, J = 14.4, 6.0 Hz, 1H), 2.51 (dt, J = 7.2, 6.7 Hz, 2H), 2.22−2.15 (m, 1H), 2.11−2.03 (m, 2H), 1.97 (ddt, J = 12.3, 4.7, 2.2 Hz, 1H), 1.70 (br s, 1H), 1.63 (dd, J = 4.7, 1.0 Hz, 3H), 1.61 (d, J = 1.2 Hz, 3H), 1.32 (s, 3H), 1.31 (dd, J = 12.4, 11.1 Hz, 1H), 1.22 (ddd, J = 11.6, 11.6, 11.6 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H) ppm; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.41 (s, 1H), 8.00 (s, 1H), 5.53 (dt, J = 15.2, 6.6 Hz, 1H), 5.44 (dt, J = 15.3, 6.4 Hz, 1H), 5.39−5.29 (m, 2H), 4.95 (d, J = 9.4 Hz, 1H), 4.46 (dd, J = 8.1, 6.2 Hz, 1H), 3.92−3.84 (m, 1H), 3.67 (d, J = 5.0 Hz, 1H), 3.54−3.47 (m, 1H), 3.22 (s, 3H), 3.02 (s, 3H), 3.05−2.97 (m, 1H), 2.89 (t, J = 7.4 Hz, 2H), 2.74−2.64 (m, 2H), 2.50 (dt, J = 7.2, 6.7 Hz, 2H), 2.11−2.00 (m, 2H), 1.97 (ddd, J = 12.4, 4.7, 1.5 Hz, 1H), 1.88 (ddt, J = 12.3, 4.5, 2.3 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H), 1.24 (s, 3H), 1.22 (dd, J = 12.3, 11.3 Hz, 1H), 1.10 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 0.95 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 155.6, 141.8, 138.1, 136.1, 135.8, 132.0, 130.4, 130.3, 129.7, 128.4, 122.5, 99.5, 72.9, 65.8, 64.6, 56.5, 47.7, 44.9, 40.5, 40.3, 35.2, 29.9, 28.2, 23.6, 23.3, 17.9 ppm; ^{13}C NMR (125 MHz, acetone-d_6) δ 166.0, 156.3, 142.2, 139.5, 137.6, 136.9, 132.6, 131.3, 130.9, 130.0, 129.6, 122.8, 100.0, 73.1, 66.4, 64.2, 56.0, 47.7, 45.8, 41.5, 41.3, 35.8, 35.7, 30.2, 28.5, 23.9, 23.3, 21.6, 17.9 ppm; IR (film) 3401, 2958, 2929, 1632, 1579, 1449, 1375, 1229, 1189, 1108, 1048, 1025, 969, 917, 830, 774 cm^{-1}; $[\alpha]_D^{25}$ = −46.8° (c = 0.635, $CHCl_3$); HRMS (CI) exact mass calcd for $C_{29}H_{42}N_2O_6Li$ [M + Li]$^+$ 521.3203, found 521.3185.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4a**, **5**, **21**−**23**, **24a**−**b**, **27**−**30**, **38**−**42**, **45a**−**b**, **46a**−**b**, **47a**, **48a**, **51**, and **54** and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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