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Total Synthesis and Structural Studies of the Antiviral Marine Natural Product Hennoxazole A

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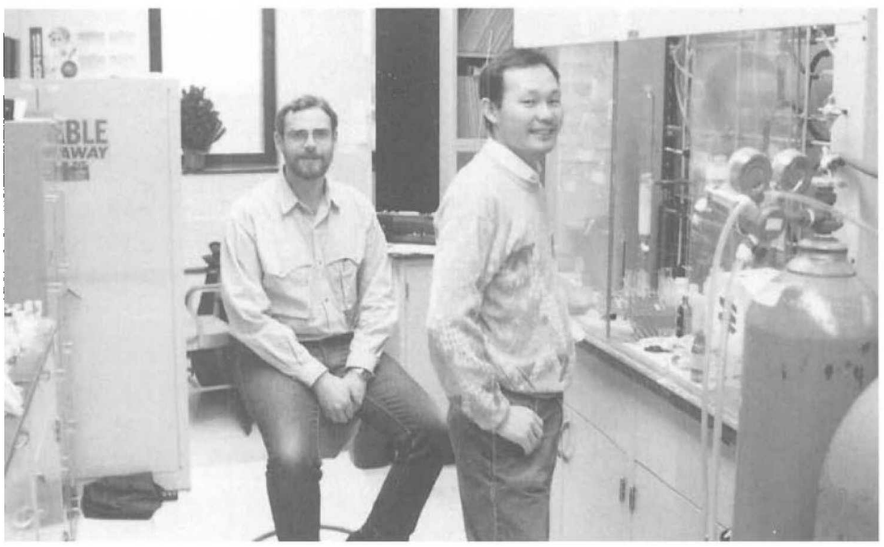

Peter Wipf received his Diploma in 1984 and his Ph.D. in 1987 from the University of Zürich under the direction of Prof. *Heinz Heimgartner* on 1,3-dipolar cycloadditions with nitrile ylides and the synthesis and conformational analysis of peptides with α,α-disubstituted amino acids. He continued his scientific eduction as a Swiss NSF Postdoctoral Fellow at the University of Virginia with Prof. *Robert E. Ireland*, where he worked on the total synthesis of FK-506 and studied the ester-enolate Claisen rearrangement. In 1990, he joined the faculty at the University of Pittsburgh as an Assistant Professor, and was promoted to Associate Professor in 1995. His current 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 investigation of C–C bond formation *via* organometallics.
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.

Abstract. A concise synthetic strategy and the structure elucidation of hennoxazole A are presented. A *meta*-xylene degradation is used to construct the pyran segment, and the preparation of the skipped polyene moiety is accomplished *via* asymmetric reduction of a β-stannyl enone, an S_N2 displacement of an allylic trimethylbenzoate with vinyl cuprate, and coupling of a vinyl-zinc reagent with a π-allyl palladium species. The final steps of the convergent total synthesis of (2*S*,4*S*,6*S*,8*S*,22*R*)-hennoxazole A involve an amide coupling followed by the construction of the bisoxazole core. The combined use of circular dichroism, total synthesis, and optical rotation serves to unequivocally establish the relative and absolute configuration of the marine natural product. A new empirical CD helicity rule is proposed that allows the assignment of bisallylic stereocenters in acyclic homoconjugated dienes. In addition, an independent proof of the configuration of hennoxazole A is based on an extensive study of *van't Hoff*'s principle of optical superposition. This chiroptical analysis employs the additivity of the molar rotation [Φ] of the individual stereocenters.

1. Introduction

Beyond the straightforward demonstration that new synthetic strategies and methodologies can successfully be applied toward complex target molecules, total synthesis has often been the basis for an unambiguous assignment of the relative and absolute configuration of natural products. This is especially true for marine natural products. Marine organisms are the source of a great variety of biologically active secondary metabolites. Often only small quantities of marine natural products can be isolated from an exploration site, and many marine species have been resistant to laboratory culturing. Since symbiotic relationships are common among marine life forms, there are even considerable ambiguities about the actual biological source of certain samples. Therefore, the evaluation of the biological potential of promising bioactive compounds frequently has to await the development of a suitable synthetic route. In addition, the small sample quantities and the unusual structural features of marine natural products make structure elucidation extremely challenging even with modern spectroscopic tools and leave doubts especially on stereochemical assignments. It is possible that more than 50% of all structures of marine natural products that were originally assigned have to be corrected upon reinspection, often after synthetic work highlights ambiguities. Therefore, the preparation of sufficient quantities of material for further studies and the proof of structure, two of the traditional major missions of total synthesis, are central contributions of synthetic chemistry to marine biotechnology [1].

Hennoxazole A (**1**) was isolated by *Ichiba et al.* from a marine sponge, a *Polyfibrospongia* sp. (*phylum Porifera*), and was shown to be highly active against herpes simplex virus (HSV-1, IC_{50} = 0.6 μg/ml) [2]. This structurally diverse natural product incorporates a bisoxazole, a pyranoid glycoside, and a skipped triene unit (*Fig. 1*). The relative configuration at C(2), C(4), and C(6) was determined by

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CHIMIA 50 (1996) Nr. 4 (April)

NMR experiments [2]; the absolute configuration as well as the relative configuration at C(8) and C(22) remained unresolved.

Several structural features of hennoxazole A attracted our immediate interest. The peptide-derived bisoxazole core of the molecule was unique and, at the time, only found in hennoxazole A and the diazonamides [3], another complex polycyclic marine alkaloid (*Fig. 2*). More recently, other directly linked bisoxazole units have been discovered in the cyanobacterium-derived muscoride A [4] and in additional members of the hennoxazole family (*Fig. 3*) [5][6].

Another structural feature of hennoxazole A that attracted our interest was its highly unusual homoconjugated triene terminus. Generally, lipophilic chains are characterized by conformational flexibility mediated by multiple methylene units. Due to the presence of three skipped alkenes, especially the *cis*-configurated trisubstituted alkene at C(20)–C(21) and the homoallylic stereocenter at C(22), we suspected that the lipophilic tail of hennoxazole A was conformationally highly preorganized and assumed a helical secondary structure. This analysis was confirmed by molecular-modeling studies [7]. Due to $A^{1,3}$ strain across the *cis*-double bond [8], the C(20)–C(23) dihedral angle is locked at about 90°, thus positioning the propenyl chain in an orthogonal position with regard to the plane of the trisubstituted alkene (*Fig. 4*). This unusual conformational bias of the lipophilic chain became crucial for the subsequent structure elucidation of the natural product, and, as we have determined in subsequent SAR studies, also appears to be an important component of the biological profile of hennoxazole A.

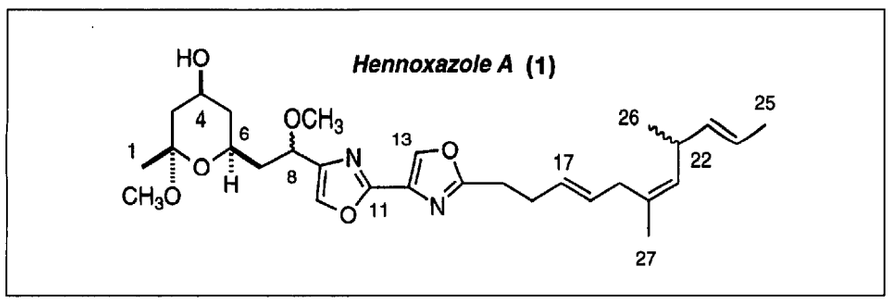


Fig. 1. *Structure of hennoxazole A*

2. Retrosynthetic Analysis

The unique structural features and the interesting biological activity of hennoxazole A encouraged us to embark on a total synthesis of the marine natural product.

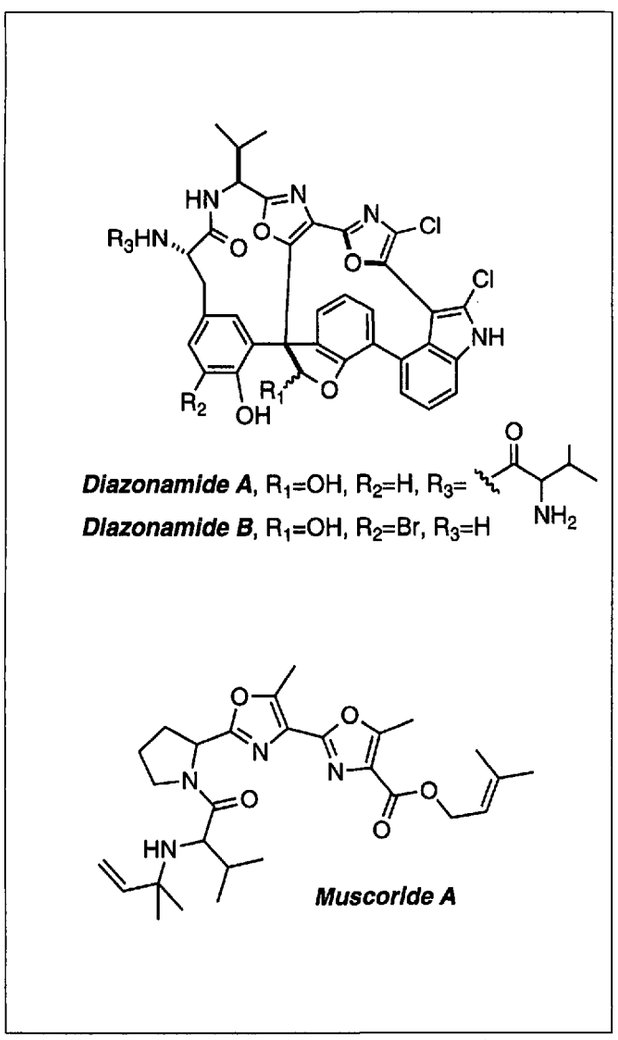


Fig. 2. *Bisoxazole natural products*

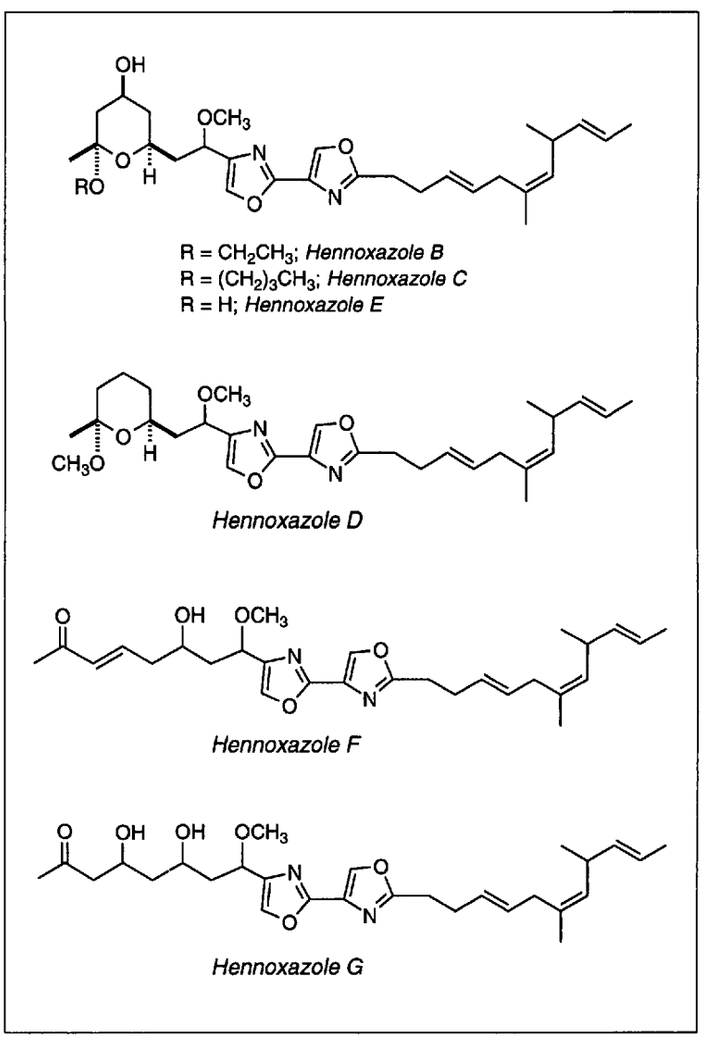


Fig. 3. *Hennoxazoles*

Since its absolute configuration as well as the relative configuration at C(8) and C(22) were unknown, the synthetic strategy had to be sufficiently concise to allow the preparation of more than one stereoisomer. An obvious retrosynthetic analysis was to dissect the target molecule into three segments, *e.g.* the pyran, bisoxazole, and triene moieties. However, this convergent analysis required manipulations of the stereocenter at C(8) at late stages of the synthesis. Even though an indirect assignment of this stereocenter by modified *Mosher* ester methodology appeared possible, some ambiguity due to the high level of functionalization of the substituents would remain, and it was not clear how easily both stereoisomers at this position were synthetically accessible. A cleavage of the molecule at C(11) maintained the convergent character of the synthesis and allowed an early, unambiguous assembly of stereocenter C(8). However, this required the formation of the bisoxazole unit at a late stage of the synthesis from amino alcohol **2** and acid **3**, an unprecedented and challenging proposal due to the acid- as well as oxidation-sensitive nature of **2** and **3** (*Scheme 1*). Encouraged by our earlier successful studies on the synthesis of oxazolines and oxazoles [9], we nonetheless decided to attempt the assembly of hennoxazole A at the bisoxazole due to the expected ease of stereochemical assignment and manipulation of segments **2** and **3**.

Similar to our syntheses of aranorosin and LL-C10037α [10], the heterocyclic portion of segment **2** was to be constructed by arene oxidation of **4**. In contrast to the multiple carbon-heteroatom bond formation in the preparation of **2**, metal-mediated C–C bond construction would be used for the synthesis of acid **3** from peptide **5**. Therefore, key features of our planned synthesis were: *1*) a highly convergent strategy that combined pyran and triene segments *via* a novel bisoxazole synthesis; *2*) the use of a *meta*-xylene as a pyran synthon; *3*) a vinyl cuprate S_N2-displacement of a sterically hindered allylic ester at C(22) [11][12].

3. Synthesis of the C(1)–C(10) Segment of Hennoxazole A

For the synthesis of the left side C(1)–C(10) segment **2** of hennoxazole A, an *Evans-Mislow* rearrangement [13] of the S-oxide of thioether **8** provided the (*E*)-allylic alcohol **9** in >96% diastereomeric purity (*Scheme 2*). The branched thioether **8** was obtained in high yield by allylation

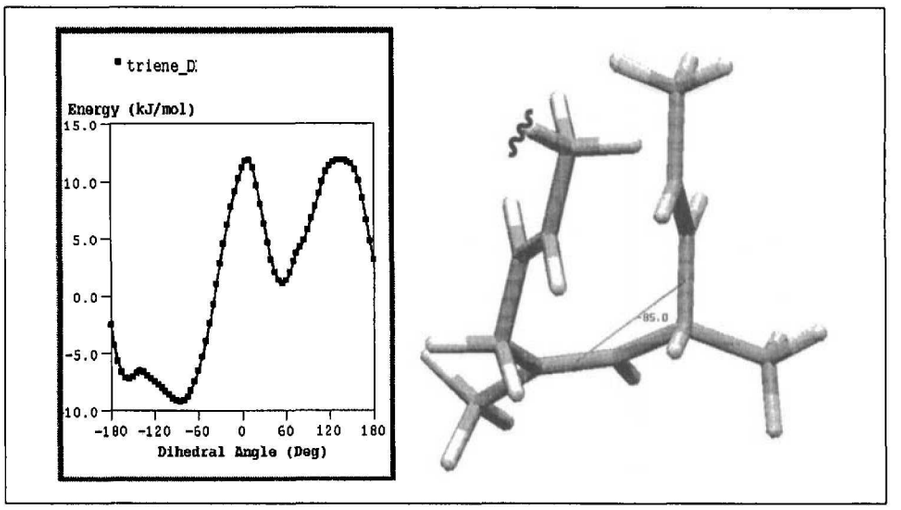
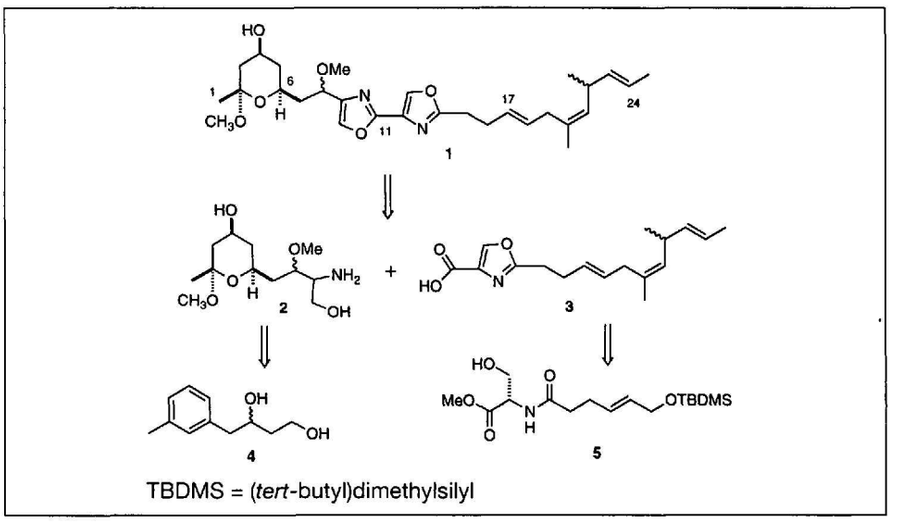
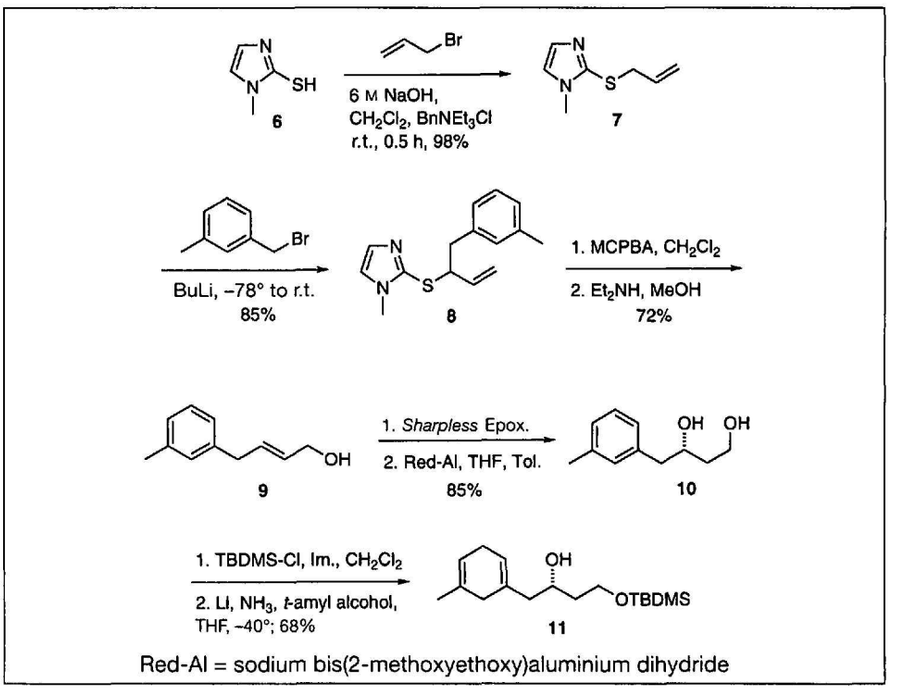


Fig. 4. *Conformational analysis of the C(16)–C(27) segment of hennoxazole A*

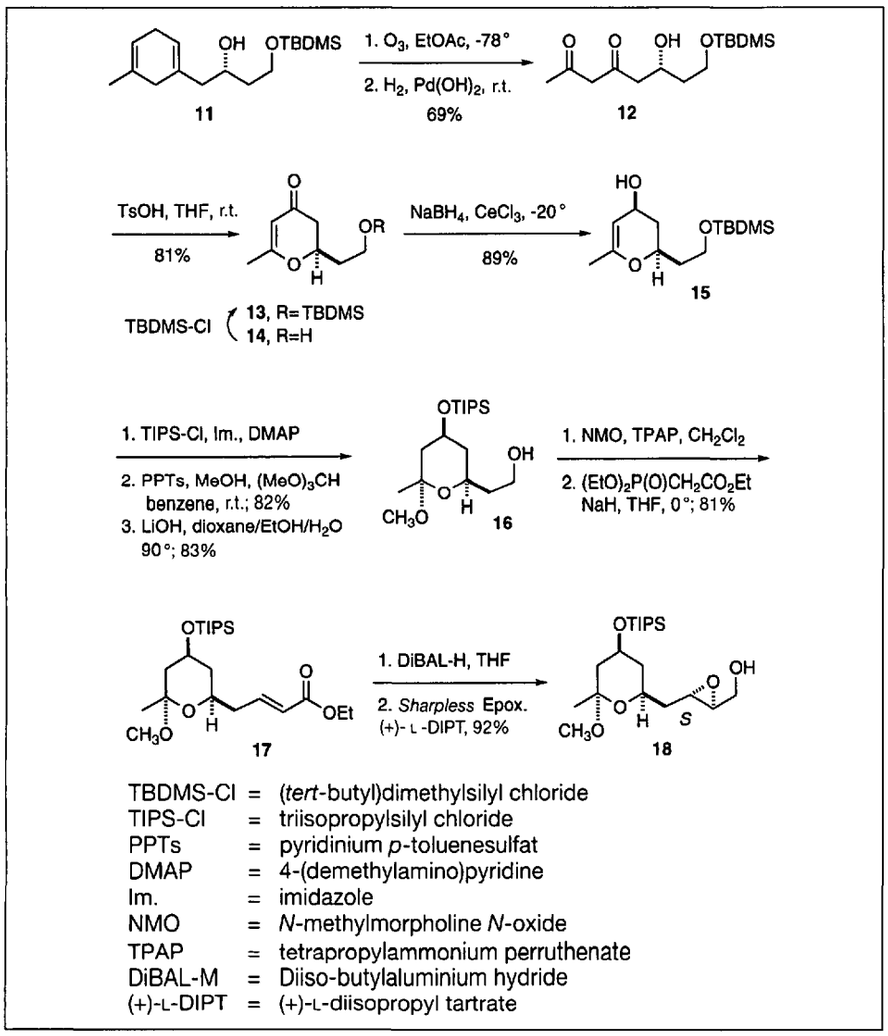
Scheme 1



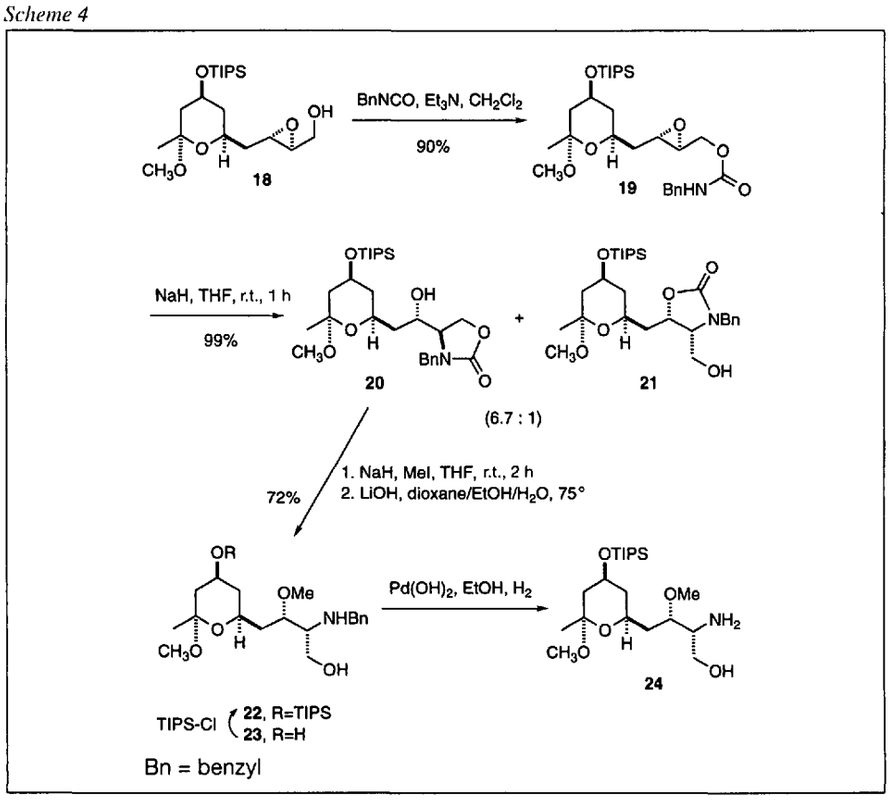
Scheme 2



Scheme 3



Scheme 4



of commercially available 2-mercapto-1-methylimidazole (**6**), followed by α-benzylation with *m*-xylyl bromide. The *Evans-Mislow* route to allylic alcohol **9** proved superior in diastereomeric purity than an alternative *Wadsworth-Emmons* condensation-reduction protocol. *Sharpless* asymmetric epoxidation [14] of **9** in the presence of (+)-L-diisopropyl tartrate followed by oxirane reduction with Red-Al [15] introduced the secondary alcohol function at C(6) that was going to be used as a linchpin for the construction of the pyran stereocenters at C(2) and C(4). The diastereomeric excess of this transformation was >96%, but the actual configuration in **10** was chosen arbitrarily. Selective silylation of the primary alcohol and dissolving metal reduction yielded the diene **11** in seven steps and 35% overall yield from **6**.

Ozonolysis of **11** followed by reductive workup completed the unraveling of the β-diketone functionality from the *meta*-substituted xylene (*Scheme 3*) [16]. After treatment of the complex mixture of keto enol as well as cyclic isomers of the intermediate 6-hydroxy-8-[(*tert*-butyl)dimethylsilyloxy]octane-2,4-dione (**12**) with *p*-TsOH in THF, 81% of a 1:1.9 mixture of pyranones **13** and **14** was isolated. Reprotection of the primary alcohol function with TBDMS-Cl converted **14** back to the desired silyl ether **13**. In spite of the loss of some of the silyl ether protective group in the cyclization of **12**, it was advantageous to perform this reaction under the more vigorous dehydrative conditions leading to glycals **13** and **14** since the subsequent 1,2-reduction of the enone with $NaBH_4$ in the presence of $CeCl_3$ [17] occurred exclusively *via* axial attack directed by the stereocenter at C(6). The resulting secondary allylic alcohol **15** was silylated with TIPS-Cl and the glycal function was solvolyzed in MeOH in the presence of PPTs and methyl orthoformate to give the desired axial anomer in 59% overall yield from **12**. Again, the methanolysis conditions had to be carefully monitored to avoid the facile elimination of the allylic silyl ether in the acidic medium. Selective cleavage of the primary TBDMS ether *vs.* the secondary TIPS ether was best accomplished under strongly basic conditions with LiOH in a ternary mixture of dioxane/ethanol/water 1:1:2.

Side-chain extension of alcohol **16** to give ester **17** proceeded in 81% yield *via* oxidation with catalytic perruthenate [18] and *Wadsworth-Emmons* reactions. DIBAL-H reduction of **17** and *Sharpless* asymmetric epoxidation of the resulting allylic alcohol in the presence of (+)-L-DIPT provided the epoxy alcohol **18** in

92% yield and >96% de. The (*S*)-configuration at C(8) was randomly selected, since no information about relative or absolute configuration of the natural product was available [19].

The protocol of *Kishi* [20] and *Roush* [21] was chosen for the introduction of the amino function at C(9) (*Scheme 4*). Treatment of **18** with benzyl isocyanate, followed by cyclization of the intermediate urethane resulted in a 87:13 mixture of isomeric oxazolidinones **20** and **21**. The desired major product **20** was purified by chromatography on SiO_2, *O*-methylated, hydrolyzed, and hydrogenated to give the amino alcohol **24**. Under the basic conditions necessary for cleavage of the oxazolidinone, some hydrolysis of the TIPS ether was unavoidable, and an easily separable 2.3:1 mixture of **22** and **23** was isolated in addition to 14% of unreacted **20**. Overall, the left side segment **24** was thus prepared in 22 steps and in 5% yield.

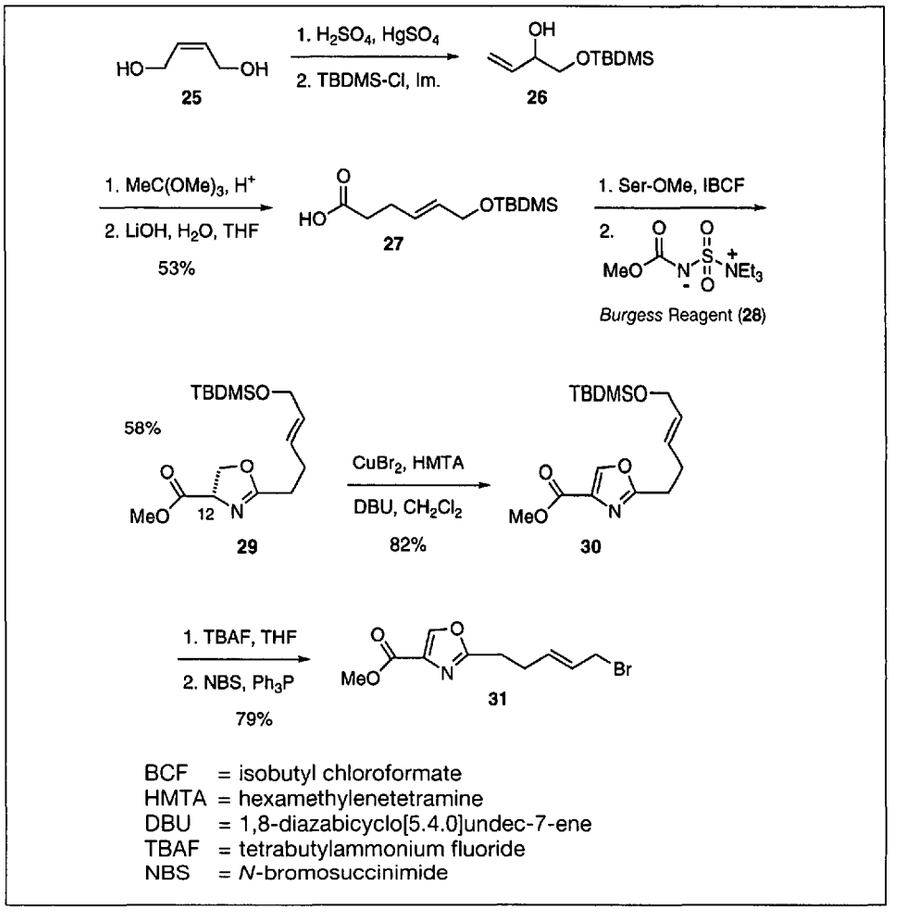
4. Synthesis of the C(11)–C(27) Segment of Hennoxazole A

Johnson orthoester *Claisen* rearrangement [22] of allylic alcohol **26** in the presence of trimethyl orthoacetate and propionic acid followed by saponification provided the building block **27** for the synthesis of the right side of hennoxazole A (*Scheme 5*). Alcohol **26** was readily obtained in large quantities by Hg^{II}-catalyzed rearrangement of *cis*-but-2-enediol (**25**) [23].

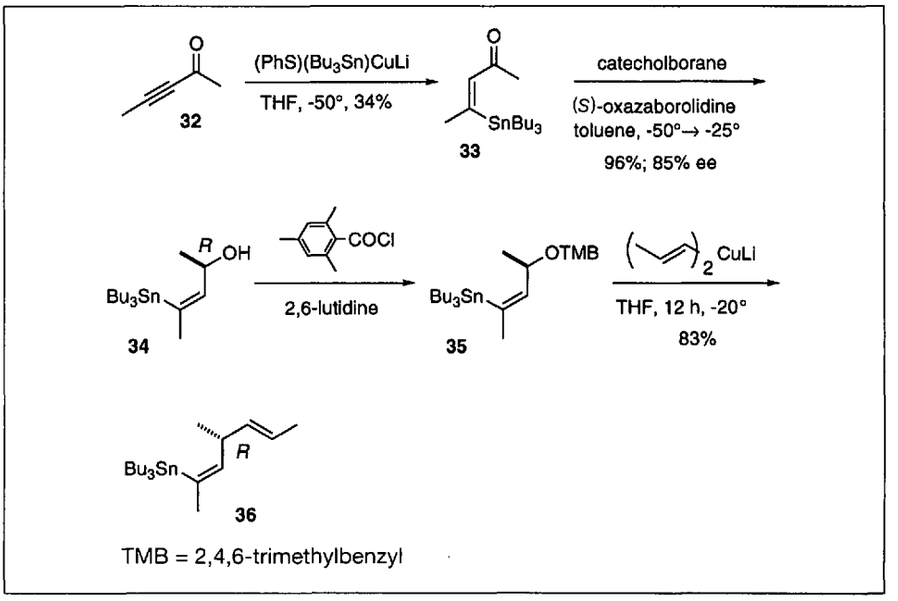
Coupling of acid **27** with the mixed anhydride derived from isobutyl chloroformate and serine methyl ester was followed by cyclodehydration [9a] with *Burgess* reagent (**28**) to give the intermediate oxazoline **29** that was oxidized to the oxazole with cupric bromide [24] in the presence of DBU and HMTA. The formation of oxazole **30** by this cyclization-oxidation pathway was possible due to the presence of the electron-withdrawing ester function at C(12) of the oxazoline (*Scheme 5*). In the absence of an electron-withdrawing functional group at this position, *e.g.* for the formation of the second oxazole ring of hennoxazole A, this protocol is extremely low-yielding (*vide infra*).

O-Desilylation and bromination [25] of the allylic alcohol led to the π-allyl palladium precursor **31**. A Pd-catalyzed coupling between allylic bromide **31** and vinyl stannane **36** was envisioned to establish an efficient access to the right side C(11)–C(25) segment of hennoxazole A. For the preparation of **36**, conjugate addition of the mixed cuprate [26] derived

Scheme 5



Scheme 6

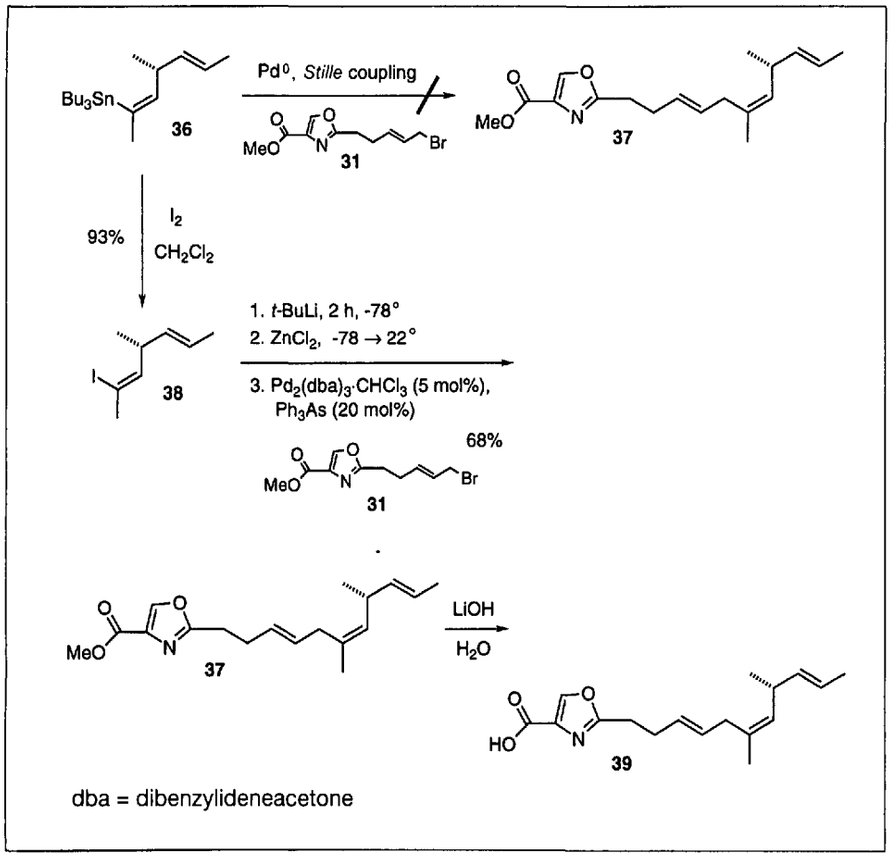


from copper(I) thiophenoxide and Bu_3SnLi to ynone **32** provided vinyl stannane **33** in 34% yield as a single geometric isomer (*Scheme 6*).

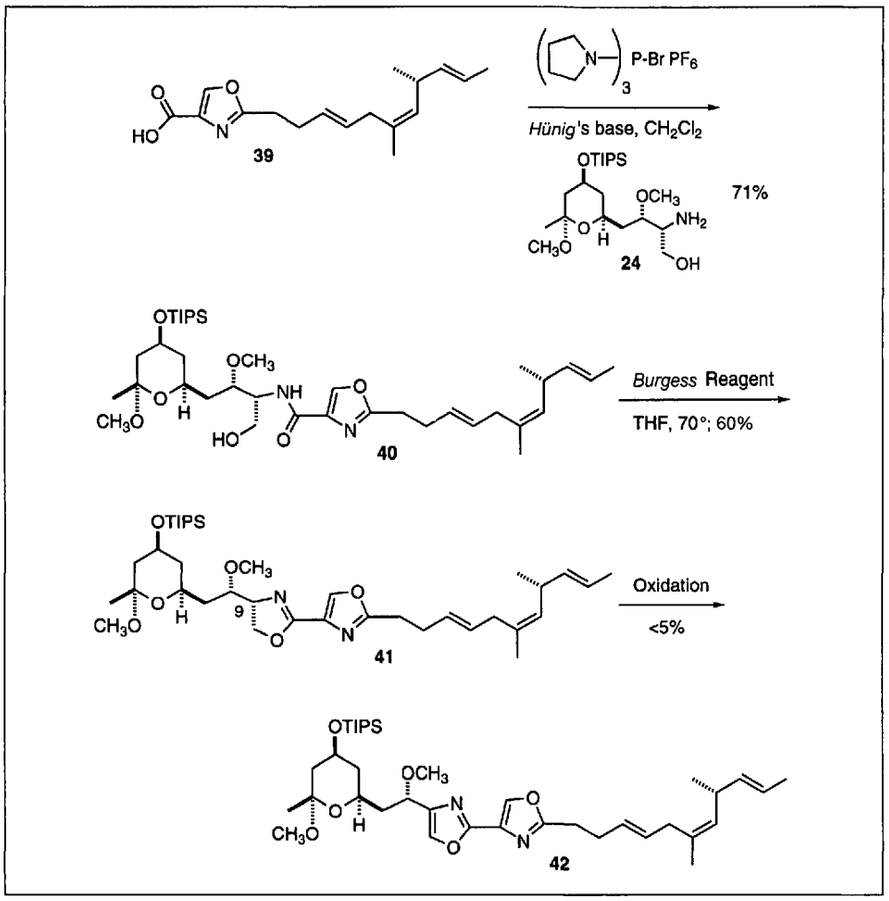
Asymmetric reduction of **33** with 20 mol% of tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane [27] in the presence of stoichiometric quantities of catecholborane [28] gave (*R*)-allylic alcohol **34** in 85% ee and 96% chemical yield. The (*R*)-configuration of **34** was arbitrarily obtained by the use of (*S*)-enantiomer of the chiral auxiliary but independently confirmed by comparison to literature data. The enantiomeric excess of the oxazaborolidine reduction

CHIMIA 50 (1996) Nr. 4 (April)

Scheme 7



Scheme 8



was determined to be 85% by *Mosher* ester analysis.

After considerable experimentation, we found that conversion of **35** to the 2,4,6-trimethylbenzoate [29] allowed a subsequent very clean S_N2 inversion with propenyl cuprate to provide the skipped diene **36** in 83% yield. Major side reactions in the use of sulfonates and unhindered esters as leaving groups in the cuprate reaction were elimination to the conjugated diene and deacylation, respectively.

Direct Pd-catalyzed coupling of the vinyl stannane **36** with allylic bromide **31** failed due to the considerable $A^{1,3}$ strain in stannane **36** which was recovered unchanged from the reaction mixture (*Scheme 7*). Interestingly, the use of **34** in the *Stille* reaction resulted in good yields of coupling product. Most likely, anchimeric assistance of the secondary HO group in the Sn→Pd transmetalation of **34** facilitated conversion of this substrate. In accordance with this theory, the use of *O*-protected derivatives of **34** in the *Stille* coupling was unsuccessful.

In spite of the lack of reactivity of vinyl stannane **36**, coupling of the corresponding vinyl-zinc reagent [30], which was obtained from **36** *via* tin-iodine exchange, metal-halogen exchange, and Li→Zn transmetalation, provided the desired triene **37** as a single isomer. The use of Ph_3As [31] as a Pd^0 co-ligand was crucial for achieving a high conversion in this reaction. After saponification, the right side segment **39** was thus prepared in a total of 14 steps from **26** and **32** and in 14% yield as calculated for the longest linear sequence.

5. Total Synthesis of (2*S*,4*S*,6*S*,8*S*,22*R*)-Hennoxazole A

The final segment condensation involved the challenging preparation of the bisoxazole moiety (*Scheme 8*). Coupling of acid **39** with amino alcohol **24** with the PyBroP reagent [32] provided amide **40** in 71% yield. As expected, oxazole synthesis *via* cyclodehydration/oxidation was unsuccessful due to the lack of a carbonyl substituent at C(9) of oxazoline **41**. With a variety of standard oxidizing agents, the yield of the desired oxazole **42** remained below 5%. Initially, the alternative oxazole synthesis from amide **40** *via* oxidation/cyclodehydration [9c] faced similar obstacles (*Scheme 9*). The highly functionalized aldehyde **43**, obtained by oxidation of **40** with *Dess-Martin* periodinane [33], was rapidly decomposed upon attempted cyclodehydration. Due to the

presence of acid-sensitive (ketal), base-sensitive (β-alkoxy aldehyde) as well as oxidation-sensitive (homoconjugated triene) functional groups in **43**, our standard reaction conditions [9c] for oxazole synthesis provided only traces of the desired **42**. After considerable experimentation, a crucial modification of this protocol was found with the use of a weak, sterically hindered base to buffer the reaction medium (*Scheme 10*).

Exposure of aldehyde **43** to 2,6-di-(*tert*-butyl)-4-methylpyridine and *in situ* prepared triphenylphosphonium halide provided the intermediate 10-bromooxazoline **44**. This bromooxazoline was subsequently dehydrohalogenated with DBU in acetonitrile, and final desilylation with TBAF provided (2*S*,4*S*,6*S*,8*S*,22*R*)-hennoxazole **45** in an overall yield of 27% from segment **39**.

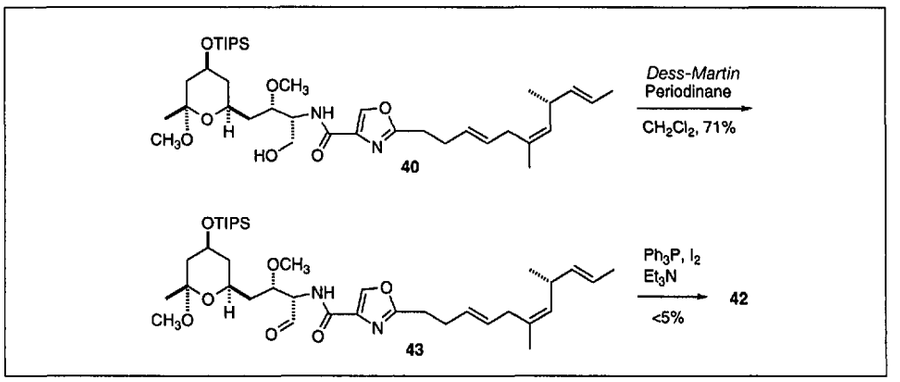
6. Structure Assignment of Natural Hennoxazole A (1)

In ^{1}H- and ^{13}C-NMR, the synthetic material **45** was identical with the natural compound, and, based on the opposite sign of its $[\alpha]_D$, it was tentatively assigned to have the enantiomeric structure [11]. However, since the configuration at several stereocenters of hennoxazole A was unknown, this conclusion was only preliminary and required further inspection. The definitive assignment of the relative and absolute configuration of natural hennoxazole A was possible by the concerted use of circular dichroism, total synthesis, and *van't Hoff*'s principle of optical superposition.

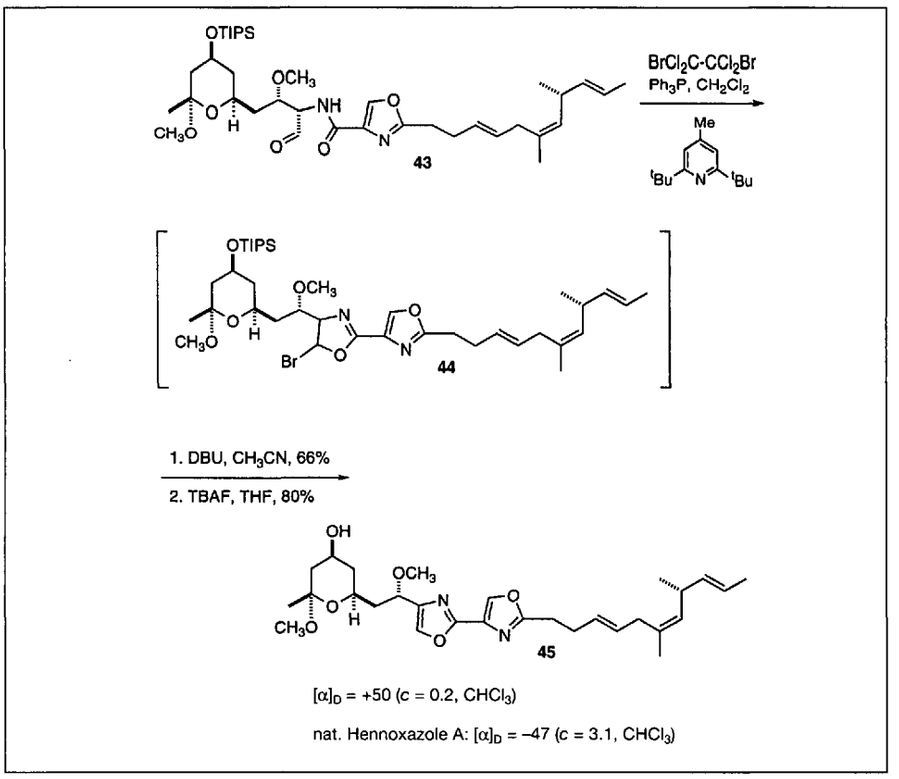
The circular-dichroism spectra of **1** and **45** displayed a strong ellipticity at 206 nm in the olefinic $\pi \rightarrow \pi^*$ transition area (*Fig. 5*). Application of the CD alkene sector rule [34] to the trisubstituted alkene moiety of **45** revealed that the larger allylic substituent, the propenyl group (R'), occupied one of the positive quadrants in the x-y-z projection of the alkene, and thus was indeed expected to elicit a positive *Cotton* effect (*Fig. 6*) [35]. Consequently, the negative *Cotton* effect at 206 nm observed for the natural compound could potentially be explained by the presence of the (22*S*)-configuration in **1**. However, a closer inspection of the CD characteristics of the homoconjugated alkene segment of hennoxazole proved this analysis to be superficial in two important aspects.

A comparison of the CD spectra of the two synthetic intermediates **34** and **36** clearly demonstrated a red-shift in combination with a very significant increase in

Scheme 9



Scheme 10



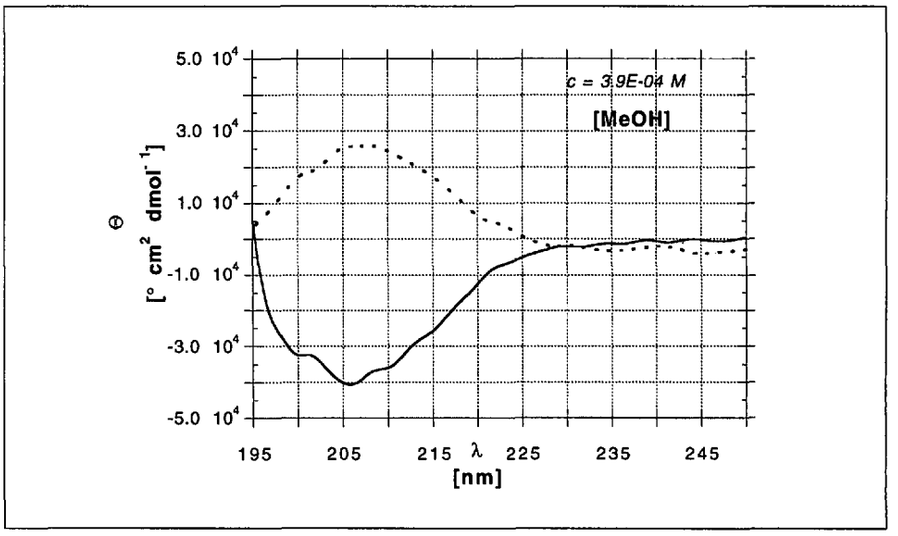


Fig. 5. *CD spectra of natural (—) and synthetic (---) (2S,4S,6S,8S,22R)-hennoxazole A*

CHIMIA 50 (1996) Nr. 4 (April)

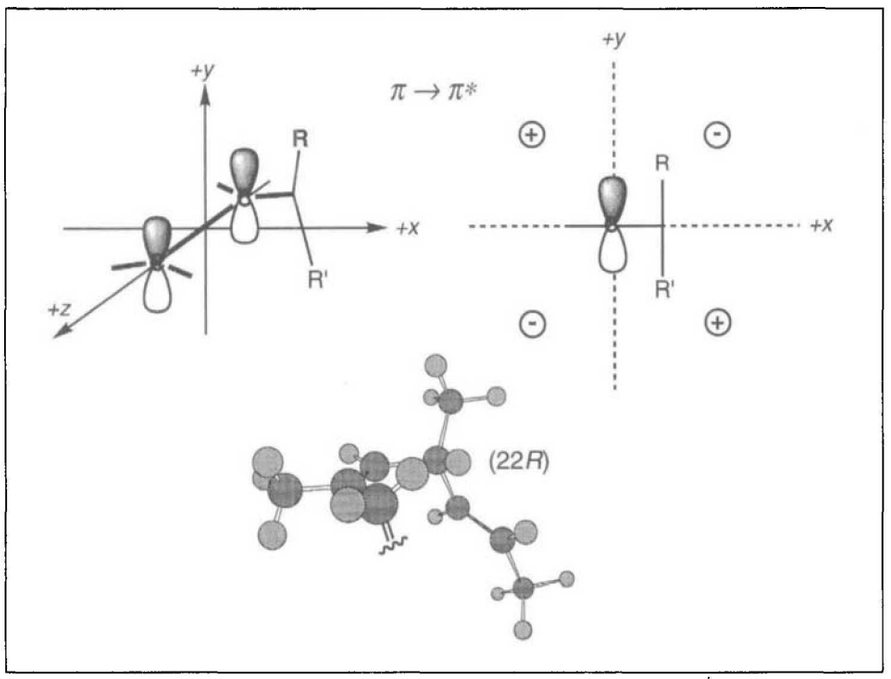


Fig. 6. *Analysis of the C(20)=C(21) trisubstituted alkene moiety of* **45** *according to the alkene sector rule*

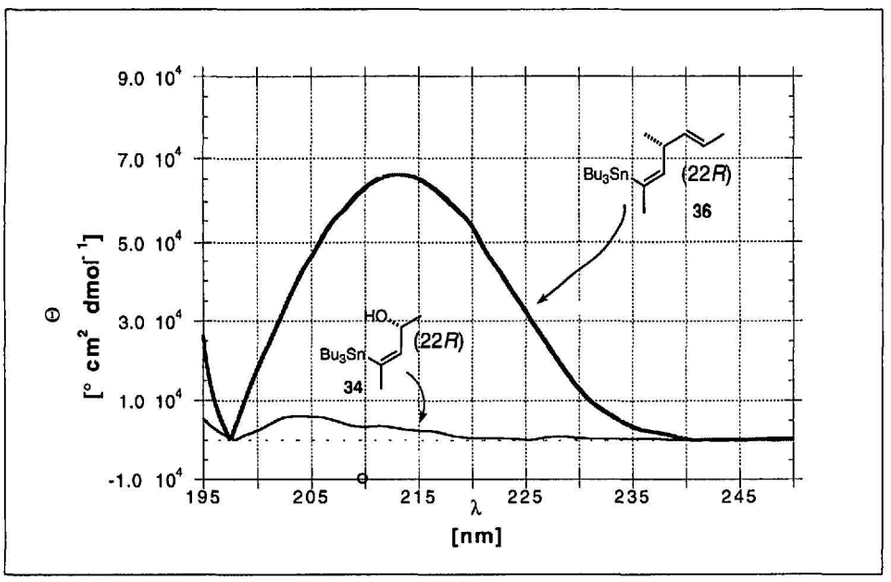


Fig. 7. *CD spectra of synthetic intermediates* **34** *and* **36**

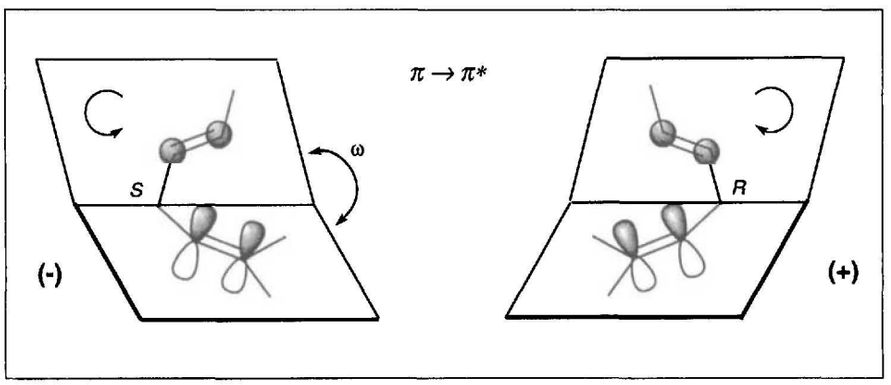


Fig. 8. *The homoconjugated diene helicity rule for the correlation of the sign of the* Cotton *effect and the configuration at the bisallylic stereocenter*

the ellipticity upon attachment of the second, homoconjugated C=C bond (*Fig. 7*). This is indicative of an oscillator coupling between the two homoconjugated alkenes in **36** [36], thus generating an inherently dissymmetric [37] chromophore. For the only asymmetrically disturbed symmetric chromophore in **34**, a much smaller, analytically not useful ellipticity was observed. The effect of homoconjugation of dienes in CD has been studied for rigid, mostly bicyclic organic molecules, but, to the best of our knowledge, this analysis has not been extended to acyclic systems [38–40]. In analogy to a model for n→π* transitions in β,γ-unsaturated ketones formulated by *Djerassi*, *Mislow*, *Moscowitz*, and coworkers [41], we propose a homoconjugated diene helicity rule for the correlation of the sign of the *Cotton* effect at the long-wavelength π→π* transition of acyclic dienes and the chirality at the bisallylic stereocenter (*Fig. 8*) [42]. A counterclockwise, negative helical movement of the π-electrons in the homoconjugated chromophore would thus be reflected in a negative *Cotton* effect and correlate with the (*S*)-configuration, whereas clockwise, positive helical movement is characteristic of a positive *Cotton* effect and an (*R*)-configuration at the bisallylic tetrahedral C-atom [43]. Naturally, any orbital mixing in such a system depends considerably on the dihedral angle ω in *Fig. 8*, with a maximum suggested for $\omega = 90°$ and a possible minimum at $\omega = 180°$. Due to the considerable allylic $A^{1,2}$ strain, this angle is conformationally restricted in *cis*-trisubstituted alkenes such as **1**, **45**, and **36**. Indeed, molecular-mechanics analysis of **1**, **45**, and **36** indicated a preference of at least 2.5 kcal/mol for $\omega = 85° \pm 15°$ [44], thus validating an application of the helicity rule for these acyclic alkenes [45].

Incidentally, use of this new CD rule with hennoxazoles led to the same conclusion as the alkene sector rule, *e.g.* confirming the (22*R*)-configuration for **45**, and suggesting a (22*S*)-configuration for **1**. However, an assignment of the single remote stereocenter of the highly functionalized hennoxazoles by this helicity rule remained questionable, since several other stereocenters and chromophores could possibly interfere with the chiroptical fingerprint of the homoconjugated diene.

Specifically to address this problem, we studied the circular dichroism of partial structures **46** and **47** (*Fig. 9*). The left side analog **47**, containing the (2*S*,4*S*,6*S*, 8*S*)-stereocenters and the C(9)–(11) oxazole function present in **45**, exhibited nonetheless a very weak ellipticity of opposite sign to **45**. In contrast, the CD of the right

side segment **46** with the (22*S*)-configuration closely corresponded to the CD of natural hennoxazole and was a mirror image of synthetic **45** with (22*R*)-configuration. This is sufficient proof that the diene helicity rule can indeed be applied for the stereochemical assignment of bisallylic stereocenters in highly functionalized molecules with multiple stereocenters such as the hennoxazoles. Due to the highly dissymmetric nature of the helical homoconjugated diene, CD spectroscopy opened a unique chiroptical window for this moiety and relegated the much weaker ellipticities of the remaining only dissymmetrically perturbed stereocenters to the background.

The CD analysis of **1**, **36**, and **45–47** allowed an unambiguous assignment of the (22*S*)-configuration for natural hennoxazole A, but it also demonstrated that CD did not provide meaningful information for the correlation of the stereocenters at C(2),C (4), C(6), and C(8). Therefore, we extended our strategy for the total synthesis of **45** toward the preparation of (2*S*,4*S*,6*S*,8*S*,22*S*)-hennoxazole **48**, (2*S*,4*S*,6*S*,8*R*,22*S*)-hennoxazole **49**, and (2*S*,4*S*,6*S*,8*R*,22*R*)-hennoxazole **50** (*Fig. 10*). Spectroscopically (^{1}H-, ^{13}C-NMR) these epimers formed two distinctive groups: **45** and **48** were identical with the natural hennoxazole A (**1**), whereas **49** and **50** were indistinguishable among each other, but very different to the first group.

From the eight possible diastereomers and enantiomers of hennoxazole A that remained after the original structure elucidation by *Scheuer* and *Higa* [2] this straightforward spectroscopic comparison in combination with the CD-based assignment of the (22*S*)-configuration further restricted the possibilities for the natural product to **48** and the enantiomer of **45**. A choice between these two isomers could now easily be made, since the $[\alpha]_D$ of natural hennoxazole A was reported, and confirmed by our measurements, to be –47 ± 2 (c = 0.1–0.5, MeOH). Since synthetic **45** and **48** were determined to have $[\alpha]_D$'s of +50 and –9.4, respectively, natural hennoxazole A was unambiguously assigned to have the relative and absolute configuration shown in *Fig. 11*, *e.g.* the enantiomer of synthetic **45**.

The combined use of spectroscopic analyses and total synthesis is a powerful tool for the unambiguous structural assignment of novel natural products with remote stereocenters, but this strategy is quite time- and cost-intensive and, therefore, only of limited general use in natural products chemistry. A closer inspection of $[\alpha]_D$ values of our hennoxazole A epimers and their synthetic segments revealed the possibility for another, independent approach for a stereochemical assignment entirely based on a very straightforward chiroptical analysis. More than 100 years ago, *van't Hoff* proposed that individual stereocenters in a chiral compound make independent contributions to the molar rotation [46][47]. In essence, this means that the configuration of molecules with multiple stereocenters can be derived by measurement of the molar rotation ($[\Phi]_D$) of the compound, if the increments of the individual stereocenters are known and arithmetically added. Relatively soon it was found that limitations to this rule existed [48], especially for carbohydrates where the directly linked stereocenters interfered with simple additivity rules (the so-called 'vicinal action limitation'), and

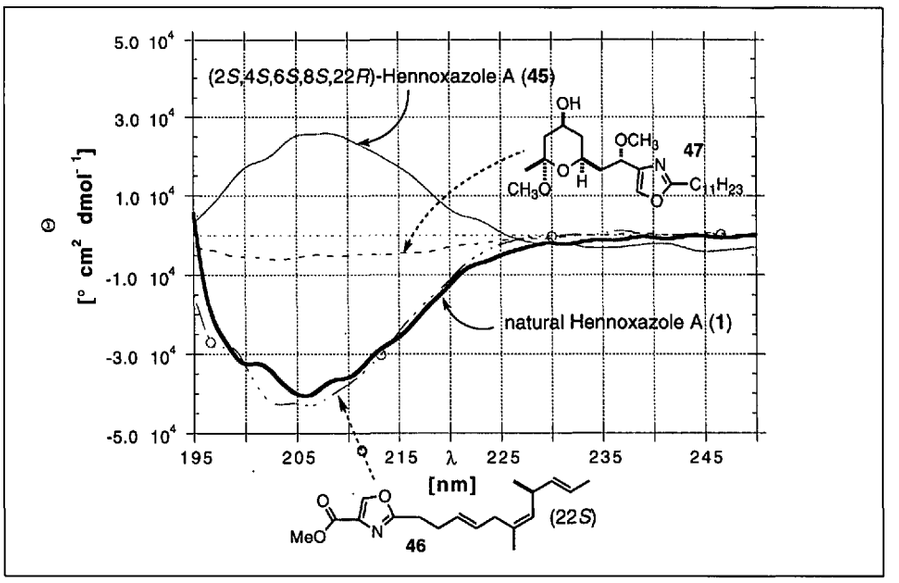


Fig. 9. *Comparison of CD spectra of hennoxazoles and partial structures.* The C(22)-stereocenter is primarily responsible for the sign and the magnitude of the *Cotton* effect at 205 nm.

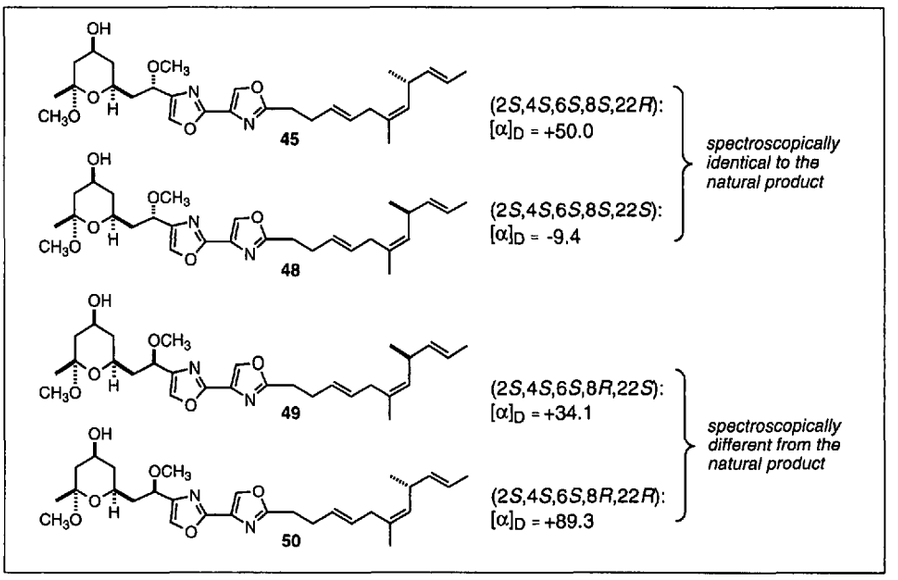


Fig. 10. *Hennoxazole isomers prepared by total synthesis*

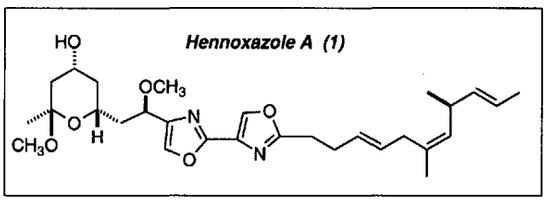
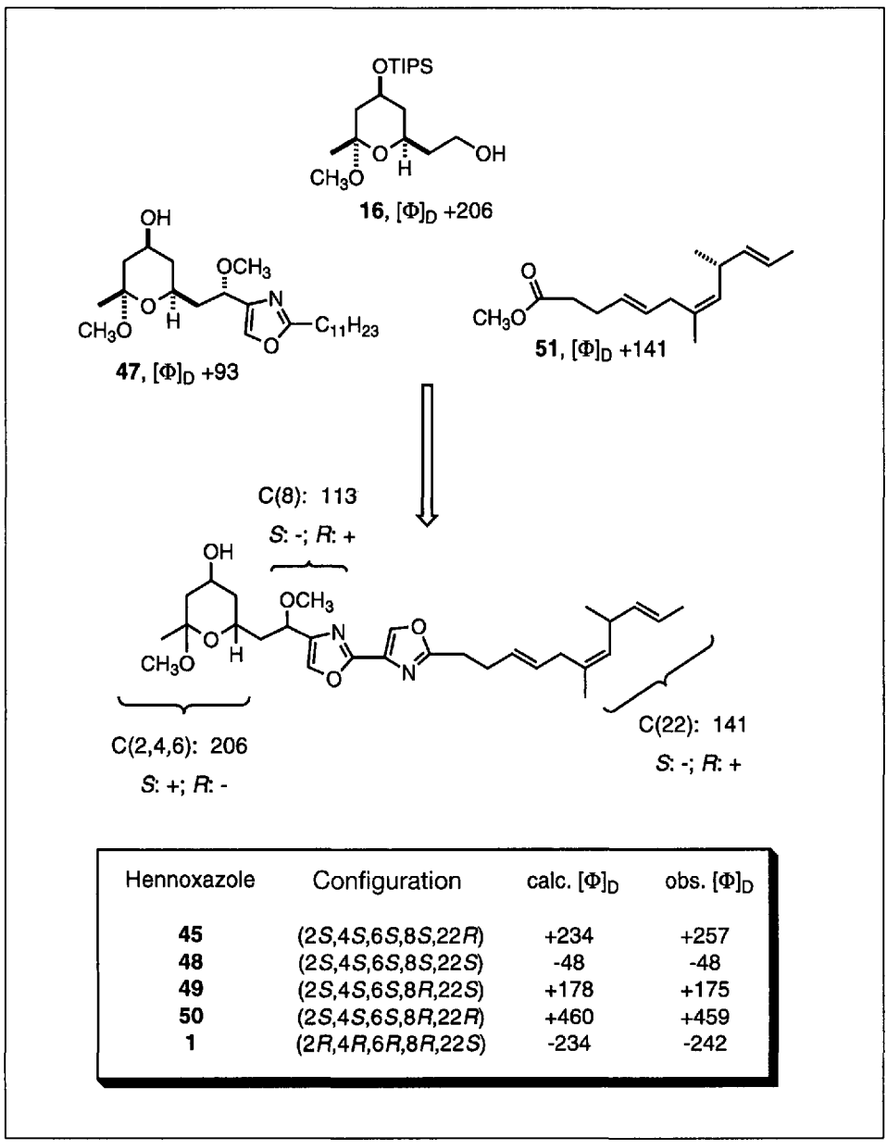


Fig. 11. *Relative and absolute configuration of natural hennoxazole A*

CHIMIA 50 (1996) Nr. 4 (April)



Hennoxazole	Configuration	calc. $[\Phi]_D$	obs. $[\Phi]_D$
45	(2*S*,4*S*,6*S*,8*S*,22*R*)	+234	+257
48	(2*S*,4*S*,6*S*,8*S*,22*S*)	-48	-48
49	(2*S*,4*S*,6*S*,8*R*,22*S*)	+178	+175
50	(2*S*,4*S*,6*S*,8*R*,22*R*)	+460	+459
1	(2*R*,4*R*,6*R*,8*R*,22*S*)	-234	-242

Fig. 12. *Stereochemical analysis of hennoxazoles based on* van't Hoff*'s principle of optical superposition and increments for the molar rotation of stereogenic carbons derived from partial structures* ***16****,* ***47****, and* ***51***

van't Hoff's principle remained somewhat of a counterintuitive curiosity in the literature [49]. However, it applies exceedingly well to hennoxazole A. The molar rotation of segments **16**, **47**, and **51** provided the necessary increments for an *a priori* calculation of $[\Phi]_D$'s for all eight diastereomers and enantiomers of hennoxazole A (*Fig. 12*) [50]. The difference between calculated and experimentally determined optical rotation was generally less than 5%, *e.g.* well within the experimental errors of the measurements, with only one exception (hennoxazole **45**), where it was relatively more significant (9%) but still small in absolute terms given the large structural differences between **16**, **47**, **51**, and hennoxazoles.

Specifically, the proposed (2*R*,4*R*,6*R*, 8*R*,22*S*)-configuration for natural hennoxazole A (**1**) led to the addition of increments of –206 (for stereocenters 2, 4, and 6), +113 (C(8)), and –141 (C(22)), *e.g.* a total $[\Phi]_D = -234$. Since the experimentally determined $[\Phi]_D$ was –242 and no other stereochemical isomers calculated close to this value (*Fig. 12*), *van't Hoff*'s principle of optical superposition successfully and unambiguously assigned the correct configuration to the marine natural product. It is important to note that this chiroptical technique is independent from the previously used CD and NMR analyses and that the necessary increments derived from structures **16**, **47**, and **51** were quite readily obtained by partial rather than total syntheses. Indeed, an early application of *van't Hoff*'s principle would have enabled us to assign the correct configuration of hennoxazole A many months before the completion of the first total synthesis of the enantiomer of this compound. Clearly, *van't Hoff*'s principle of optical superposition is an extremely powerful tool for stereochemical assignment and has been considerably underutilized in natural products chemistry. Paired with the asymmetric synthesis (or literature $[\Phi]_D$ search) of appropriate small fragments, it can rapidly establish the structure of complex acyclic target molecules.

7. Conclusion

The first total synthesis of the antiviral marine natural product hennoxazole A has established new synthetic strategies and methodologies for the preparation of highly functionalized bisoxazoles. In addition, we have unequivocally assigned the relative and absolute configuration of hennoxazole A by a concerted application of circular dichroism, total synthesis, and specific optical rotation data. A new empirical CD rule has been proposed that allows the assignment of bisallylic stereocenters in acyclic homoconjugated dienes. In addition, further independent proof of the configuration of hennoxazole A was based on *van't Hoff*'s principle of optical superposition. Due to the availability of a large number of synthetic intermediates and diastereomers of the natural product by total synthesis, our study of the application of *van't Hoff*'s principle is solidly based on experimental evidence and clearly demonstrates the great potential of this chiroptical rule for the determination of relative and absolute configuration of complex natural products. Our group is actively pursuing further experimental and theoretical studies in this area.

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