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The *N*-Acyloxyiminium Ion Aza-Prins Route to Octahydroindoles: Total Synthesis and Structural Confirmation of the Antithrombotic Marine Natural Product Oscillarin

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Abstract: The first enantiocontrolled total synthesis of the marine natural product oscillarin is described. The proposed structure and absolute configuration of oscillarin is thus confirmed, and a previously assigned structure of a subunit was shown to be incorrect. The X-ray structure of an oscillarin−thrombin complex was resolved at 2.0 Å resolution, which validated its potent inhibitory activity against the enzyme with an $IC_{50} = 28$ nM. Methodology was developed for the synthesis of enantiopure octahydroindole-2-carboxylic acids with usable functionality at C-6. The method consists of the halocarbocyclization of *N*-acyloxyiminium ions containing an olefinic tether in the presence of tin tetrachloride or tin tetrabromide. This *N*-acyloxyiminium ion aza-Prins carbocyclization proved to be general for the construction of octahydroindole and perhydroquinoline 2-carboxylic acids. Mechanistic rationales are based on an antiperiplanar attack of the terminal alkene on the iminium ion, leading to an incipient secondary carbocation which is trapped by halide via an equatorial attack. X-ray crystal structures of products corroborate the expected stereochemistry.

Introduction

The linear marine peptides generally known as the aeruginosins[1] are structurally unique secondary metabolites produced by various blue-algal species of prokaryotic aquatic microorganisms.[2] Originally isolated from the cyanobacterium species *Microcystis aeruginosa*, the first member of this structural class of marine linear peptides possessing serine protease inhibitory activity was aeruginosin 298A.[1a,3] Initially, two total syntheses provided definitive evidence for its revised structure and absolute configuration.[4,5] Since then, other aeruginosins,[6] and related compounds,[7] have been isolated, their structures determined, and synthesized.[8] A third synthesis of aeruginosin 298A was recently reported.[8a]

As a class, several aeruginosins share a common 1-aza[4.3.0]-bicyclic core unit. Thus, the (2*S*,3*aS*,6*R*-hydroxy,7*aS*) octahydroindole 2-carboxylic acid core (L-Choi) is linked to a D-amino acid in combination with a D-phenyllactic acid or its substituted variants (Figure 1). Depending on the type of aeruginosin, the carboxyl end forms an amide bond with a 1-amino-ω-guanidino alkyl motif. The serine protease inhibitory activity of the aeruginosins can be related to the presence of three binding domains that can be recognized by the S_1, S_2, and S_3 sites in thrombin. X-ray crystallographic studies[3,6a] of complexes with trypsin and functional analogies with known inhibitors have validated this assumption and extrapolated it to thrombin as well.

We recently described the first total synthesis and structural confirmation of dysinosin A,[9] **1** isolated from a new genus of sponge of the family *Dysideidae* (Lizard Island, Queensland, Australia).[10] In addition to its inhibitory activity against

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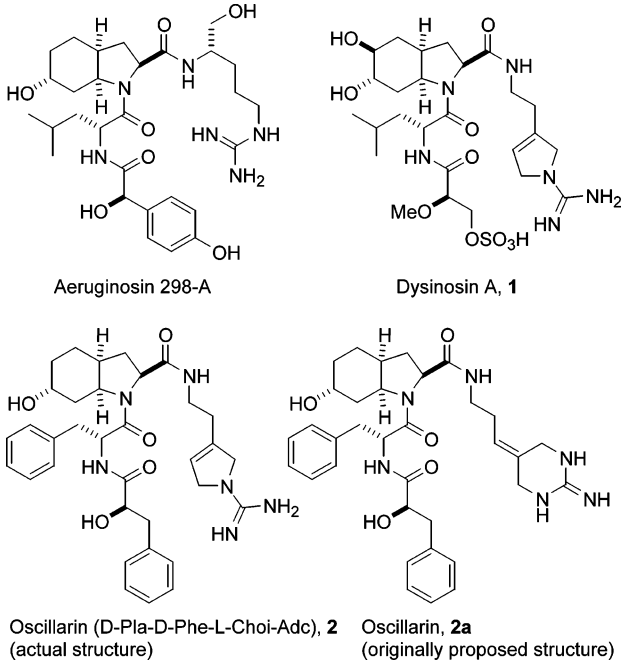

Figure 1. Structures of aeruginosin 298A, dysinosin A **1**, oscillarin (D-Pla-D-Phe-L-Choi-Adc) **2** and an originally presumed structure **2a**.

thrombin[11] and Factor VIIa, which are essential components in the blood coagulation cascade,[12] dysinosin A differs from all aeruginosins by the presence of a 5*S*,6*S*-diol in the octahydroindole-2-carboxylic acid subunit, a unique 1-(*N*-amidino-Δ^3-pyrrolino)-ethyl side chain in place of an acyclic guanidine, and an *O*-sulfated D-glyceric acid instead of aromatic counterparts (Figure 1).[13]

We now report on the first total synthesis and structural confirmation of oscillarin **2**, a hitherto little known new member of the aeruginosin family, also designated as D-Pla-D-Phe-L-Choi-Adc. Oscillarin was isolated from the algal cultures of *Oscillatoria agardhii* (strain B2 83), at the Institute of Plant Physiology of the University of Göttingen. Its structure and absolute configuration were proposed on the basis of NMR data and a partially resolved cocrystal complex with trypsin.[14] Two biogenetic and structural features concerning oscillarin are worthy of note. First, cultures of *Oscillatoria agardhii* obtained in Japan[15] are known to produce aeruginosin 205A, which was originally proposed to contain a 6*R*-chloro substitutent in the octahydroindole-2-carboxylic acid subunit. However, this structural assignment has been questioned on the basis of definitive synthesis of the proposed 2-carboxy-6-chlorooctahydroindole.[16]Second, the acyclic 1-amino-4-guanidino butyl subunit which is linked as an amide in all known aeruginosins is replaced by a 1-amino-2-(*N*-amidino-Δ^3-pyrrolinyl)ethyl group (Figure 1). In this regard, dysinosin A **1**[9,10] and oscillarin **2** are among a handful of known natural products that contain hydroxylated octahydroindole cores with a common arginine mimetic P_1 recognition site for serine protease activity, even though their respective source microorganisms live and flourish oceans apart.[13] Suomilide,[7a] a glycosidic azabicyclo[3.3.1] variant of oscillarin and dysinosin A isolated from *Nodularia spumigena HKW*, contains the same 1-amino-2-(*N*-amidino-Δ^3-pyrrolinyl)ethyl group as an amide linkage.

The structure of oscillarin **2** was originally proposed with a six-membered cyclic guanidine subunit, as shown in expression **2a**,[17] rather than the actual Δ^3-pyrroline counterpart. To the best of our knowledge, this discrepancy has never been corrected by the same group.[14,17]

Previous syntheses of the L-Choi subunit in the aeruginosins have relied on a clever utilization of L-tyrosine as a chiral progenitor,[18,19] as well as on other methods.[8a,20] Although the methodology that was developed for the corresponding unit in dysinosin A[9] could be used to access L-Choi, by performing a selective deoxygenation at C_5, we opted for a new approach that exploits a seldom used *N*-acyloxyiminium ion aza-Prins cyclization,[21] which leads directly to 6-halo-octahydroindole 2-carboxylic acids.

Results

Enolate alkylation of the dianion derived from dimethyl *N*-Boc-L-glutamate relying on 1,3-induction[22] afforded enantiopure **4** in excellent yield (Scheme 1). Cyclization to the corresponding pyroglutamate **5**, protection, and partial reduction of the lactam carbonyl gave the hemiaminal acetate **6**. Subsequent treatment with tin tetrabromide[23] effected cyclization within 5 min at −78 °C to give the desired aza[4.3.0]-bicyclic motif **7** in 78% yield. The stereochemistry at C_6 was suggested from detailed ^{1}H NMR analysis and was subsequently confirmed

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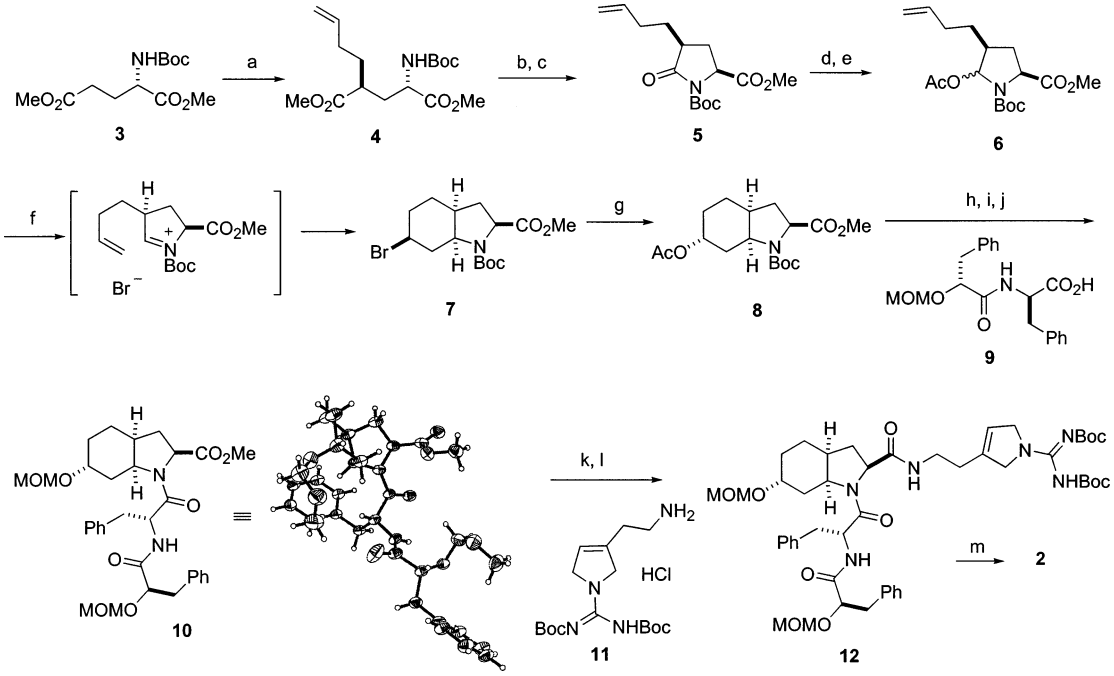
Scheme 1 [a]

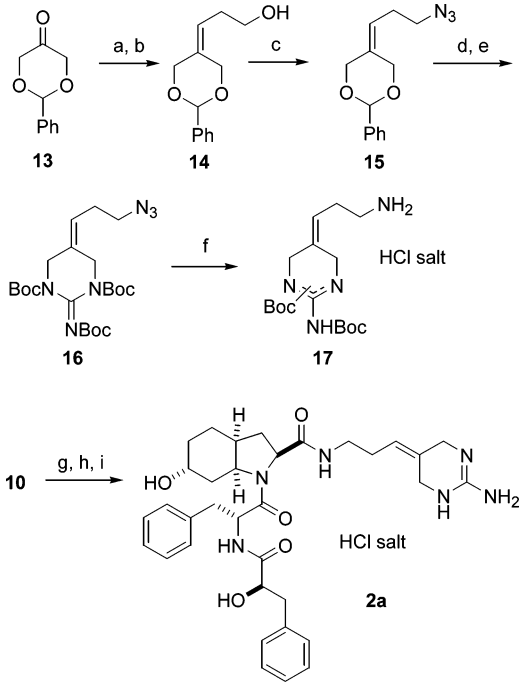


[a] a: LiHMDS, THF, −78 °C, then 3-butenol triflate, 85%; b: TFA, CH_2Cl_2 then toluene reflux, 92%; c: Boc_2O, Et_3N, DMAP, CH_2Cl_2, 90%; d: $LiBHEt_3$, THF, −78 °C; e: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 91% (two steps); f: $SnBr_4$, CH_2Cl_2, −78 °C, 78%; g: Bu_4NOAc, toluene, 40−50 °C, 78%; h: TFA, CH_2Cl_2, then EDC, HOBt, **9**, CH_2Cl_2, 91% (two steps); i: NaOMe/MeOH; j: MOMCl, $^iPr_2NEt$, CH_2Cl_2, 80% (two steps); k: LiOH, H_2O/THF; l: EDC, HOBt, Et_3N, **11**, 86% (two steps); m: aq HCl/THF 6N, 70%.

by a single-crystal X-ray structure of an advanced intermediate (Scheme 1). Displacement of the bromide with tetra-*n*-butylammonium acetate in toluene at 50 °C afforded the desired L-Choi subunit **8** in excellent overall yield (36% over nine steps from L-glutamic acid). Amide formation with a preformed MOM-protected D-phenyllactyl-D-phenylalanine **9**,[24] followed by deacetylation, and protection gave the corresponding bis-MOM ether **10**. A single-crystal X-ray structure analysis confirmed the absolute configuration of this advanced intermediate, clearly showing the axial orientation of the *O*-MOM group, the expected cis-ring junction, and confirming the structure of the originally proposed *N*-acyloxyiminium aza-Prins cyclization product. Ester cleavage, followed by coupling with 2-(*N*,*N*′-bis-Boc-*N*-amidino-Δ^3-pyrrolino)-ethylamine **11**[9] gave the penultimate precursor **12**. Deprotection under acidic conditions and purification by preparative reverse phase HPLC, afforded oscillarin **2** as the hydrochloride salt, showing spectral data identical to that reported for the natural product.[14,17]

Before we became aware of the discrepancy in the structure of the guanidine-containing motif in oscillarin, we had embarked on a synthesis route leading to the originally proposed six-membered guanidine variant (Figure 1, **2a**).[17] The synthesis started with the readily available acetal **13**, which was subjected to a Wittig reaction to give **14** (Scheme 2). Mesylation of the primary alcohol and displacement with azide gave **15**, which was deprotected and the resulting diol was subjected to a double Mitsunobu reaction with tri-*N*-Boc guanidine[25] leading to **16**. Reduction of the azide group under Staudinger conditions[26] afforded a regioisomeric mixture of cyclic bis-*N*-Boc guanidine

Scheme 2 [a]



[a] a: 3-triphenylphosphoniumpropanol bromide, BuLi, THF, −20 °C, TMSCl, then **13**; b: TBAF, THF, 75%; c: MsCl, $^iPr_2NEt$, CH_2Cl_2, then NaN_3, DMF, 50 °C, 85%; d: AcOH (80% in water); e: DEAD, PPh_3,CH_2Cl_2, tris(Boc)guanidine, 50% (two steps); f: PPh_3, H_2O, then AcOH, then Dowex 1 × 8−50 (Cl^-), 60%; g: LiOH, H_2O/THF; h: EDC, HOBt, Et_3N, **17**, 70% (two steps); i: aq HCl/THF 4N, 60%.

derivative **17**. With the precursor ester **10** already in hand, we proceeded with its coupling to **17** and deprotection as described for **12** to afford the initially presumed "oscillarin", **2a**. Not surprisingly, it was found to have no activity when tested against

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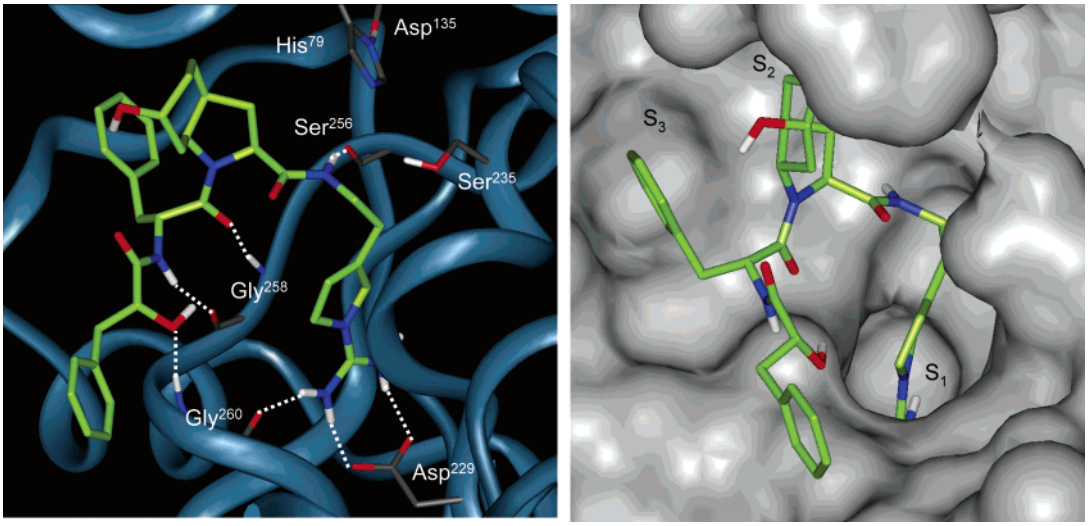

Figure 2. Left: Ribbon representation of thrombin−oscillarin complex at 2.0 Å resolution. Right: Connolly surface representation of thrombin−oscillarin complex.

α-thrombin.[27] Although the guanidine subunit in **2a** is isomeric with that in **2**, it clearly does not fulfill the requisite alignment as an arginine mimetic within the S_1 subsite of thrombin.

We were successful in obtaining a ternary complex of **2** with the α-thrombin−hirugen complex,[28] that was amenable to an X-ray structure elucidation at a resolution of 2.0 Å (Figure 2). Oscillarin forms an extended H-bonding pattern in the complex similar to the previously observed complexes reported for aeruginosin 298A[3,9] and dysinosin.[10] The P_1 arginine mimetic forms a salt bridge with the carboxylate of Asp 229 at the S_1 site. The amide NH from the octahydroindole carboxamide forms a H-bond with the backbone carbonyl oxygen of Ser 256. The Phe amide carbonyl and the amide NH are H-bonded to the amidic subunit of Gly 258, in an antiparallel *β*-strand fashion. The terminal hydroxyl forms a H-bond with the backbone amide nitrogen of Gly 260.

The octahydroindole unit delineates the P_2/S_2 interaction by stacking toward Trp 86 and Tyr 83. No interactions were observed with the 6-hydroxyl group of the Choi unit. The phenyl group of the P_3 unit points toward the S_3 hydrophobic site of the enzyme. No interactions were observed between the terminal phenyl moiety and the enzyme. This might explain why the side chain was poorly defined in the electron density. The crystal structure of oscillarin-bound thrombin is only the third for a member of the aeruginosin family.[3,10] In this context, oscillarin is the most potent inhibitor of thrombin among the aeruginosins, with an $IC_{50} = 28$ nM.

Intramolecular *N*-Acyloxyiminium Aza-Prins Cyclizations. The chemistry of *N*-acyloxy and related *N*-substituted iminium ions has a rich legacy in the realm of nitrogen-containing heterocyclic compounds.[21] Indeed, the scholarly contributions of the Speckamp, Overman, and Hart groups over the past two decades have laid a strong foundation for exploiting the synthetic applications of *N*-acyliminium ions, particularly for alkaloids and other complex nitrogen-containing natural products.[29,30] The mechanistic basis for reactions involving *N*-acyliminium ions has also invoked fundamental principles involving stereoelectronic effects,[30] and allylic strain,[31] particularly when dealing with cyclic systems.

There are several examples that involve intramolecular attack of a nucleophilic olefinic tether onto an endocyclic iminium cation for the construction of azabicyclic ring systems.[21] However, with few exceptions, they involve *ω*-unsaturated nucleophilic carbon chains tethered to nitrogen that undergo endo aza-Prins *N*-acyliminium ion type cyclizations (Figure 3A). Such cyclizations lead to azabicycles in which the nitrogen atom is at the junction of the two rings as in pyrrolizidinones, indolizidinones, quinolizidinones, and related compounds. The intermediate carbenium ions are usually solvolytically trapped in the medium by a Lewis acid or by loss of a hydrogen.[32] As already pointed out by Fisher and Overman in 1990,[33] there are fewer examples of intramolecular cyclizations in which the olefinic tether is attached to a distal carbon in an endocyclic iminium ion ring[34] (Figure 3B). Alternative pathways for the construction of monocyclic and bicyclic *N*-containing compounds utilizing iminium ion intermediates rely on cationic azonia-Cope rearrangements[21,35,36] or activation of the nucleophilic tether via vinylsilane or allylsilane chemistry.[37] The Overman and Hart groups in particular have exploited azonia-Cope and *N*-acyliminium ion cyclization chemistry in the synthesis of complex natural products.[38]

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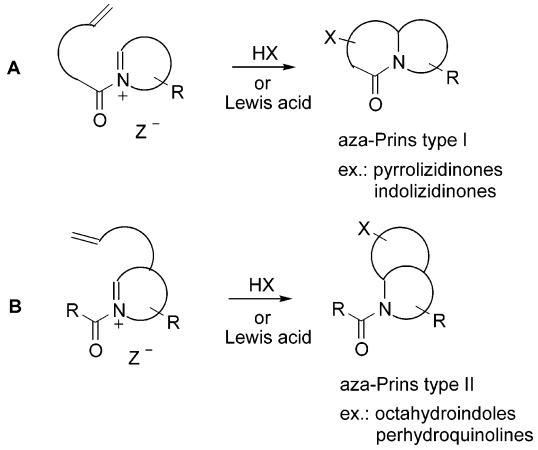
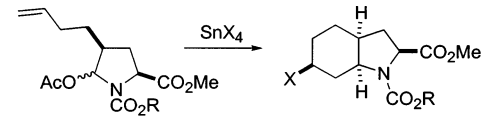


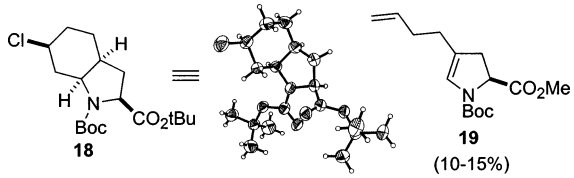
Figure 3. *N*-Tethered (A) and *C*-tethered (B) intramolecular aza-Prins-*N*-acyliminium ion type cyclizations.

There are ample examples of Lewis acid or protic acid promoted intramolecular Prins reactions[39] proceeding through oxocarbenium ions for the formation of halo-oxacycles with excellent stereocontrol.[23,40] Seminal contributions by Speckamp,[41] Overman,[42] and more recently Rychnovsky[23,43] and their respective groups have demonstrated the utility of Prins or so-called oxonia-Cope variants in natural product synthesis.

Scheme 3. Variation of the Lewis Acid and *N*-carbamoyl Group in The Formation of the Octahydroindole Cores



6a-e	7a-e
a R= t-Bu; X= Cl	66%
b R= Bn; X= Cl	60%
c R= Bn; X= Br	61%
d R= Me; X= Cl	66%
e R= Me; X= Br	72%



In contrast, there are no examples of analogous Lewis acid promoted *N*-acyloxyiminium aza-Prins halocyclizations, whereby an ω-olefinic carbon tether attached as an integral part of the ring undergoes cyclization onto an incipient endocyclic *N*-acyliminium ion with incorporation of a halogen in a 1-azabicyclic ring system related to the octahydroindoles or decahydroquinolines (Figure 3B, X = Cl, Br).[44]

As already shown in the synthesis of oscillarin, the method is a novel way to prepare 6-halo-octahydroindole-2-carboxylic acids.[16] The alternative solvolytic method with formic acid[34] would not be compatible because of the presence of the acid-labile *N*-Boc group.

The Scope of the *N*-Acyloxyiminium Aza-Prins Halocarbocyclization. Having demonstrated the utility of an intramolecular aza-Prins carbocyclization as a novel stereocontrolled route to the 6-halo(or hydroxy)-2-carboxy-octahydroindole core of oscillarin and related aeruginosins, we studied the scope and limitations of related reactions.

First, we wished to study the influence of the carbamoyl group as well as the nature of the Lewis acid on the stereoselectivity of the halocarbocyclization. We were intrigued to find that in contrast to the two Lewis acids used, the nature of the *N*-carbamoyl group had little influence on the yield or stereoselection (Scheme 3). The single-crystal structure of the *tert*-butyl ester analogue[24] of the major product **18** is shown as an Ortep diagram (Scheme 3). Clearly, $SnBr_4$ was superior to $SnCl_4$

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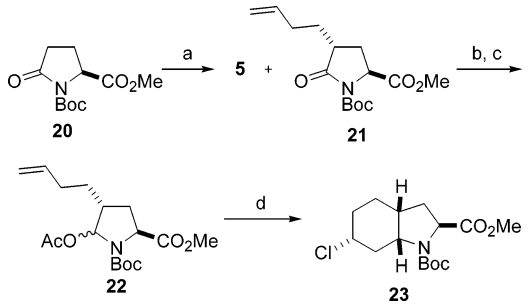
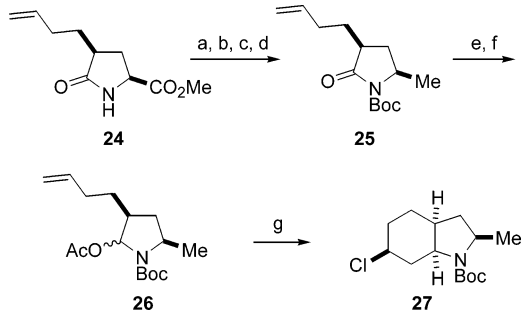
Scheme 4 [a]



[a] a: LiHMDS, THF, −78 °C, then 3-butenol triflate, 70% (1:1.8 anti/syn); b: $LiHBEt_3$, THF, −78 °C; c: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 87% (two steps); d: $SnCl_4$, CH_2Cl_2, −78 °C, 64%.

Scheme 5 [a]



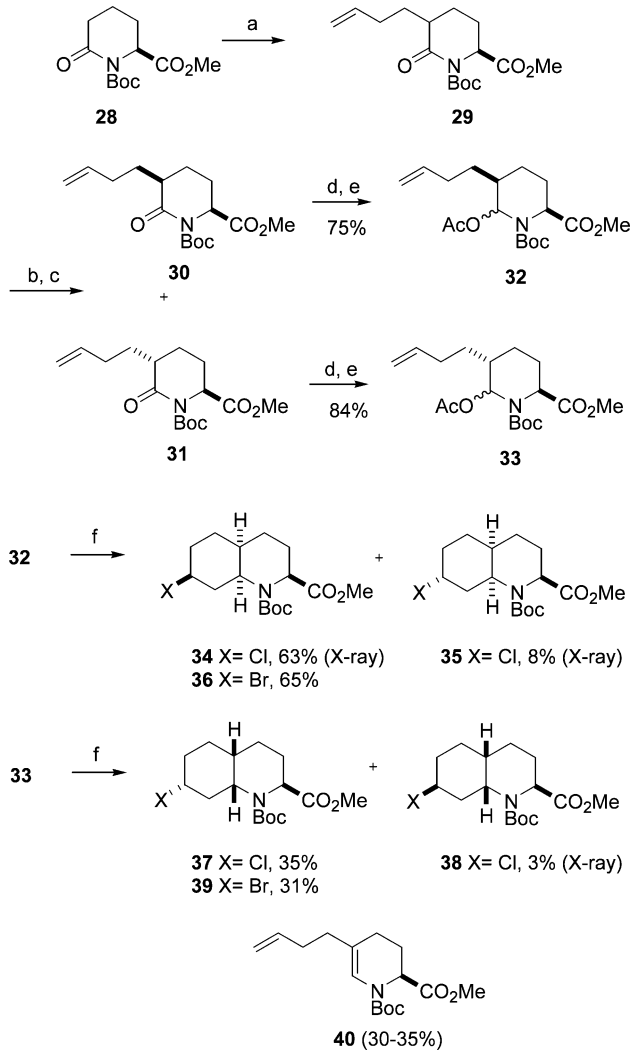
[a] a: $NaBH_4$, EtOH, 87%; b: CBr_4, PPh_3, cyclohexene, MeCN; c: Bu_3SnH, AIBN, toluene, 80 °C; d: Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35% (three steps); e: $LiBHEt_3$, THF, −78 °C; f: Ac_2O, Et_3N, DMAP,CH_2Cl_2, (80% two steps); g: $SnCl_4$, CH_2Cl_2, −78 °C, 60%.

to promote the cyclization. Interestingly, a small amount (4−5%) of *β*-acetoxy group was incorporated instead of Cl at the six position in the case of $SnCl_4$.[24] We next studied the influence of substrate concentration and the nature of the Lewis acid on the carbocylization. Using concentrations ranging from 0.01 to 0.2 M of **6** did not appreciably alter the yield of the major product or the accompanying formation of enecarbamate **19** (15−20%). The proportion of the latter increased substantially when $SbCl_5$, TMSCl, or $BF_3{\cdot}Et_2O$ were used. While there was no reaction in the presence of $ZnCl_2$, a complex mixture resulted in the case of $TiCl_4$. The halocarbocyclizations with $SnCl_4$ or $SnBr_4$ were essentially complete in a few minutes at −78 °C.[34d]

The analogous cationic carbocyclization was also successfully accomplished with the 4-epimeric series (Scheme 4). Thus, enolate alkylation of *N*-Boc-methyl-L-pyroglutamate **20** with 1-butenyl triflate gave a mixture of syn- and anti-products which could be readily separated into their 4-epimeric analogues **5** and **21**. Transformation of **21** to the corresponding *N*-Boc carbinolamine acetate **22** as previously described for **6**, and carbocyclization with $SnCl_4$ afforded the 6-chloro-octahydroindole analogue **23** in 64% yield. To eliminate any involvement of the electron-rich methoxylcarbonyl (ester) group in coordinatively participating in the delivery of halide ion, we carried out the carbocylization with the corresponding *C*-methyl lactam **25** via its activated carbinolamine derivative **26** (Scheme 5). The 6-chloro analogue **27** was formed in 60% yield, accompanied by 12% of enecarbamate.

We next studied the *N*-acyloxyiminium aza-Prins halocarbocyclizations of C-5 epimeric 6-acetoxy-L-pipecolic acid analogues, readily available from 6-oxo-*N*-Boc L-pipecolic methyl ester **28**, via enolate alkylation and separation of syn-

Scheme 6 [a]



[a] a: LiHMDS, THF, −78 °C, then 3-butenol triflate, 90% 1.3:1(anti/syn); b: TFA, CH_2Cl_2; c: Boc_2O, Et_3N, DMAP, CH_2Cl_2, 78% (two steps); d: $LiBHEt_3$, THF, −78 °C; e: Ac_2O, Et_3N, DMAP, CH_2Cl_2; f: SnX_4, CH_2Cl_2, −78 °C.

and anti-products **30** and **31**, respectively. Conversion to the acetoxy derivative **32**, followed by cyclization in the presence of $SnCl_4$, gave the corresponding bicyclic 6-*S*-chloro analogue **34** and 6*R*-epimer **35** in 63% and 8% yields, respectively, accompanied by ∼10−15% of the enecarbamate **40**. Their structures and absolute configuration were ascertained by single-crystal X-ray analysis (see below). With $SnBr_4$, only the major cyclization product **36** was isolated with the enecarbamate as a byproduct (∼10%). In contrast, cyclization of the trans-intermediate **33** under the same conditions led to only a modest yield of the corresponding chloride **37** or bromide **39** (Scheme 6). A minor epichloro isomer **38** was also isolated and characterized by single-crystal X-ray analysis. Considerable amounts of the enecarbamate **40** (30−35%) were isolated in these reactions.

Extension of the aza-Prins halocarbocyclization to generate bicyclo 1-aza[3.3.0] or bicyclo 1-aza-[3.4.0] systems from chain-shortened, that is, 4-(1-propenyl), or chain-elongated, that is, 4-(1-pentenyl)-analogues of **6**, resulted in the formation of enecarbamates with no trace of cyclization. Variations in the

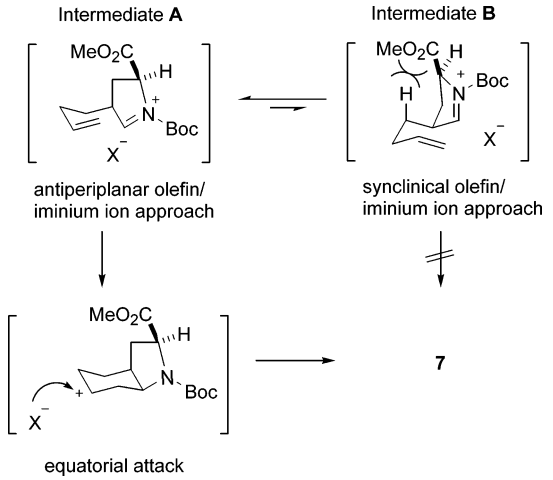


Figure 4. Proposed reactive intermediates in the *N*-acyloxyiminiumion aza-Prins halocarbocyclization to octahydroindoles.

stereochemical outcome of related cyclizations depend on the length of the carbon tether.[36]

Mechanistic Rationales. As previously mentioned, stereoelectronic control[30] during the intramolecular *N*-acyloxyiminium ion cyclizations plays an important role in deciding preferred trajectories of approach of the tethered alkenic nucleophile. It is generally agreed that maintaining maximum orbital overlap of the alkenyl π systems with the developing lone pair on the nitrogen in five- and six-membered *N*-acyloxyiminium ions is an important requirement.[30a,45] Added to this crucial control element are nonbonded interactions that could affect the conformations of reactive intermediates when bicyclic systems are involved.[29b] Thus, excluding intramolecular delivery of halide ions from carbonyl-coordinated species, a plausible mechanism for the stereocontrolled formation of 6-halo-octahydroindoles such as **7** and **23** (Schemes 1, 4, 5) is to assume an antiperiplanar alignment of the olefin and the iminium ion in a chairlike intermediate in which $A^{1,2}$ strain is minimized.[31] The halide ion would attack the incipient carbocation preferentially from an equatorial trajectory to give the major product **7** (Figure 4A). The alternative reactive conformer involving a synclinal attack (Figure 4B) in which $A^{1,2}$ strain can also be avoided would be less favored. Evidently, the minor β-acetoxy byproduct must arise from attack by the released acetate group. The higher yield when $SnBr_4$ was used may reflect the better nucleophilicity nature of bromide versus chloride ion. The same rationales apply to the formation of the major product **23** in the C_4-epimeric series (Scheme 4).

The results in the perhydroquinoline series derived from the C_2-C_5 cis-isomer **32** follow the same line of reasoning (Scheme 5). An antiperiplanar olefin approach leads to the 1-aza cis-decalinoid carbenium ion which is trapped by halide ion in an equatorial mode (Figure 5A). The single-crystal X-ray structure of the major product **34** shows a chair−chair conformation with a pseudoaxial methoxycarbonyl (ester) group in accord with minimization of $A^{1,2}$ strain. The crystal structure of the minor epimer **35** (not shown) also reveals a chair−chair conformation, a pseudoaxial methoxycarbonyl (ester) group, and an axial chlorine substituent. Thus, in this series, favorable stereoelectronic effects and minimization of $A^{1,2}$ strain are cooperative features. Although none of the epi-6-bromo isomer could be found in the case of $SnBr_4$, the difference in yield was not as important as in the octahydroindole series.

In sharp contrast, the C_5-epimeric series starting with **33** led to only modest yields of cyclized products regardless of the nature of the halide in the Lewis acid. The crystal structure of the minor cyclization product **38** depicts a chair−chair conformation in which the methoxycarbonyl (ester) group now occupies a pseudoequatorial orientation (Figure 5B). Assuming the prevalence of an iminium ion conformation in which the methoxycarbonyl (ester) group is indeed pseudoequatorial, we can project a favorable antiperiplanar approach leading to a

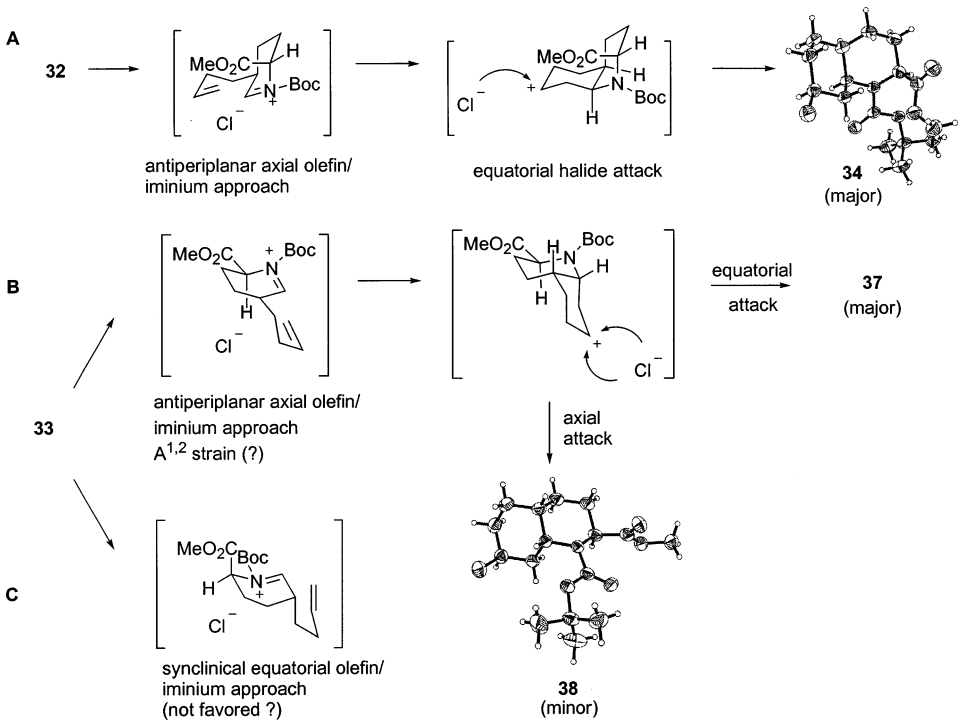


Figure 5. Proposed reactive intermediates in the *N*-acyloxyiminium ion aza-Prins halocarbocyclizations to perhydroquinolines.

carbocation that is trapped by halide attack in an equatorial or axial mode to give **37** or **38**, respectively. Despite such a favorable stereoelectronic alignment, the energetic penalty for $A^{1,2}$ strain in the reactive conformation (and product) is presumably too high. Thus, elimination to the enecarbamate competes with cyclization. The alternative conformer in which $A^{1,2}$ strain could be avoided (Figure 5C) must adopt an unfavorable synclinal approach of the olefin toward the iminium ion. Thus, both pathways from **33** are disfavored to different extents, hence the higher propensity for elimination to enecarbamate compared to **32**. No dihydrooxazinones[33] were formed in these cyclizations and the stereochemistry of the ring junction was invariably cis.

Conclusion

We have described the first enantiocontrolled total synthesis of the marine natural product oscillarin thereby confirming its revised structure and absolute configuration. A previously proposed structure containing a cyclic guanidine-containing subunit disclosed as **2a** in a patent was also synthesized and found to be incorrect. Oscillarin **2** is a potent inhibitor of the enzyme thrombin whereas the previously presumed product **2a** is inactive. A ternary complex of oscillarin and α-thrombin-huridin was resolved at a resolution of 2.0 Å.

A key reaction in the synthesis of the octahydroindole-2-carboxylic acid core relied on a seldom used *N*-acyloxyiminium ion aza-Prins halocarbocyclization. The scope of this reaction was general for diastereomeric octahydroindole-2-carboxylic acid precursors, and its versatility was shown for the synthesis of enantiopure 7-haloperhydroquinoline 2-carboxylic acids.

Octahydroindole and perhydroquinoline cores are integral subunits of biologically relevant nitrogen-containing natural products.[31,46] Important classes of therapeutic agents contain an octahydroindole or related bicyclic system.[47] The methodology developed in this work should provide easy access to these two classes of bicyclic nitrogen heterocycles harboring useful and diverse functionality for further manipulation to natural and unnatural products.

Acknowledgment. This paper is dedicated to Professors Nico Speckamp, Larry Overman, and David Hart for their seminal contributions to *N*-acyliminium chemistry. We thank NSERC for generous financial assistance through the Medicinal Chemistry Chair program. We are grateful to Dr. Kenneth Granberg and co-workers at AstraZeneca, Mölndal, Sweden for the enzyme inhibitory assays. We thank Michel Simard for the X-ray analysis of compounds shown in Schemes 1, 3, 6, and Figure 5, and Dalbir Sekhon for LC/MS assistance. M.T. is grateful for NSERC and FRNTQ fellowships.

Note Added after ASAP. In the version posted 4/16/04, there were errors in compound numbers in Scheme 4, in the 3rd paragraph of the Introduction, and in the 12th and 17th paragraphs of the Results. The version posted 4/20/04 and the print version are correct.

Supporting Information Available: Experimental procedures of key reactions, NMR, and X-ray and other data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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