CHAPTER THREE

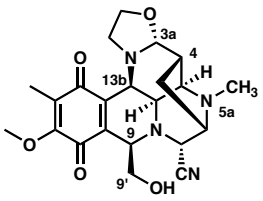
Progress Toward the Synthesis of (+)-Cyanocycline A

3.1 First Generation Approach Toward (+)-Cyanocycline A

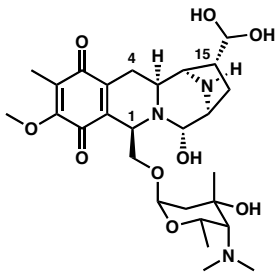
Synthetic Challenges and Structural Comparison to (–)-Lemonomycin

Cyanocycline A (**2**) presents the synthetic chemist with a host of challenges, including polar groups, sensitive functionality, and difficult stereochemical arrays (Figure 3.1).[1,2] The hexacyclic, caged structure contains eight stereocenters, including five contiguous stereogenic carbons around the piperidine ring. Three basic amines and a primary alcohol contribute polarity and sensitivity to oxidative conditions, while the quinone, aminonitrile, and oxazolidine are vulnerable to both reduction and hydrolysis.

Figure 3.1 Structural Comparison of Cyanocycline A and Lemonomycin



Cyanocycline A (2)



Lemonomycin (1)

Structurally, cyanocycline A bears both striking similarities to and important differences from lemonomycin (**1**).[3] Both compounds contain a tetrahydroisoquinoline-5,8-dione ring system fused to a 3,9-diazabicyclo[3.2.1]octane core. Additionally, both compounds exhibit hydroxymethyl functionality at C(1) of the tetrahydroisoquinoline (C(9) by cyanocycline numbering), and the absolute and relative stereochemistry around

much of the core structure is identical. However, cyanocycline A is distinguished from lemonomycin by the presence of a bridging oxazolidine ring that incorporates C(3a) and connects to C(13b) of the tetrahydroisoquinoline. To allow this connection, the stereochemistry at C(4) is epimeric to that at C(15) of lemonomycin, and C(13b) is one oxidation state higher than C(4) of lemonomycin. Conspicuously absent in cyanocycline A is the glycosyl unit of lemonomycin, as the C(9') hydroxyl is unsubstituted. Further, cyanocycline A bears a methyl group at N(5a), which is absent from lemonomycin, and has an aminonitrile in place of the carbinolamine of lemonomycin.

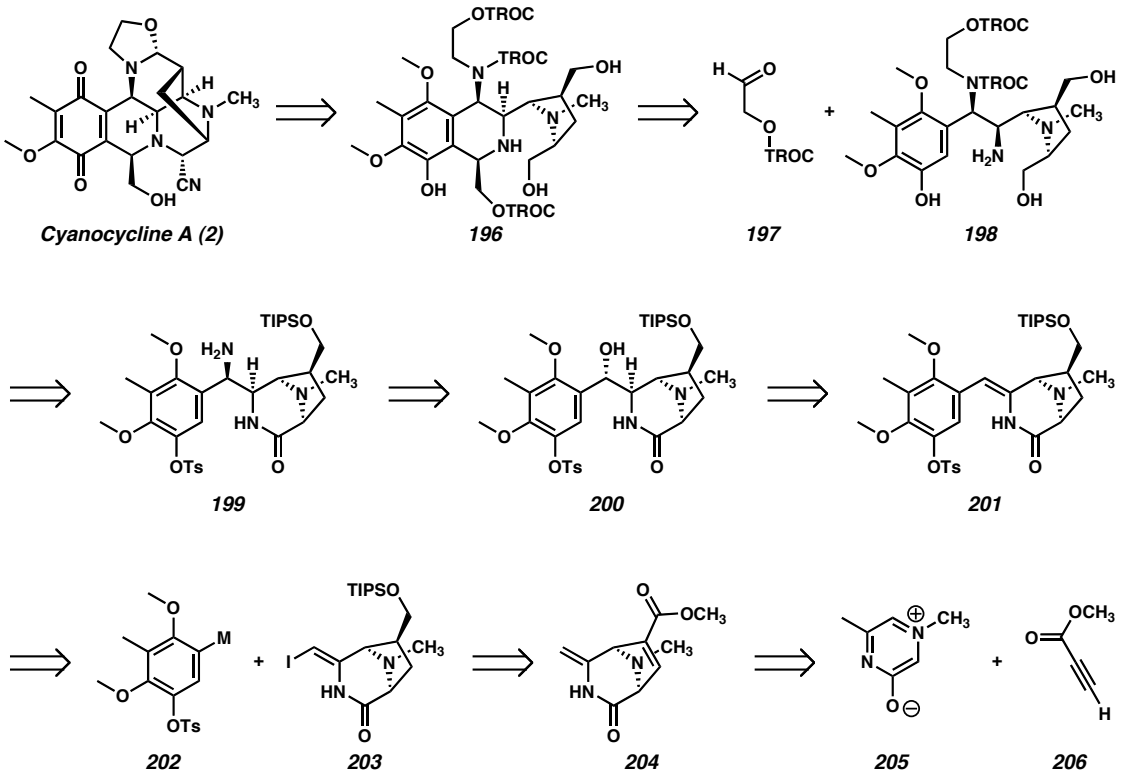
Retrosynthetic Analysis: Silyl Ether Route

To address the synthetic challenges of cyanocycline A, we planned to draw heavily on the knowledge garnered in our total synthesis of (–)-lemonomycin.[4] We therefore planned to utilize a dipolar cycloaddition, a palladium-catalyzed coupling reaction, and a Pictet-Spengler cyclization as the major carbon-carbon bond-forming reactions. However, the synthetic plan had to be altered to account for the differences between the cyanocycline and lemonomycin structures. To solve these challenges, we developed and pursued two strategies for the synthesis cyanocycline A.

Our first retrosynthetic analysis simplified cyanocycline A by deprotection and oxidation transforms to tetrahydroisoquinoline **196** (Scheme 3.1). Retro-Pictet-Spengler cyclization then revealed aminotriol **198** and protected hydroxyacetaldehyde **197**. Aminotriol **198** was disconnected through retrosynthetic reductive amination and amide reduction to amine **199**. This amine was expected to be available by Mitsunobu displacement from alcohol **200**, which could in turn be simplified to enamide **201** by

application of epoxidation and reduction transforms.[5] Enamide **201** was further simplified by retrosynthetic palladium coupling to unveil arene **202** and iodoenamide **203**. We planned to synthesize iodide **203** by stereoselective reduction,[6] protection, and iodination from diazabicycle **204**. Lastly, implementation of a dipolar cycloaddition transform led to dipole **205** and methyl propiolate as starting materials for the synthesis.

Scheme 3.1 Retrosynthetic Analysis of Cyanocycline A



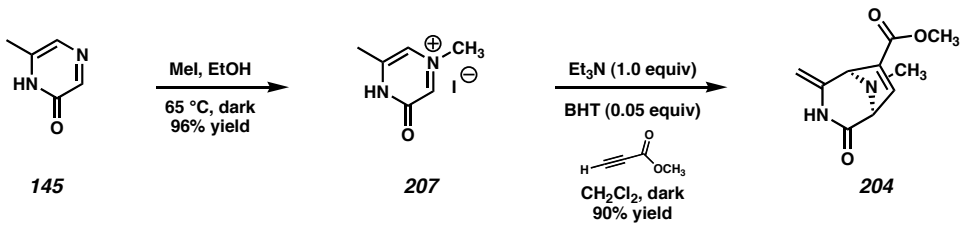
This retrosynthetic analysis addresses the differences between cyanocycline A and lemonomycin through both the use of alternative starting materials and unique transformations. The N(5a) methyl group appears as the *N*-methyl of dipole **205**, while the use of aldehyde **197** in the Pictet-Spengler cyclization resolves absence of lemonose

from the cyanocycline framework. The problem of the epimeric relationship between C(4) of cyanocycline and C(15) of lemonomycin is rectified through a diastereoselective olefin reduction of diazabicycle **204**. Lastly, the sequence of enamide oxidation, Mitsunobu inversion, and reductive amination installs the correct oxidation state at C(13b) and provides the necessary atoms for the oxazolidine ring.

Synthetic Progress Along the Silyl Ether Route

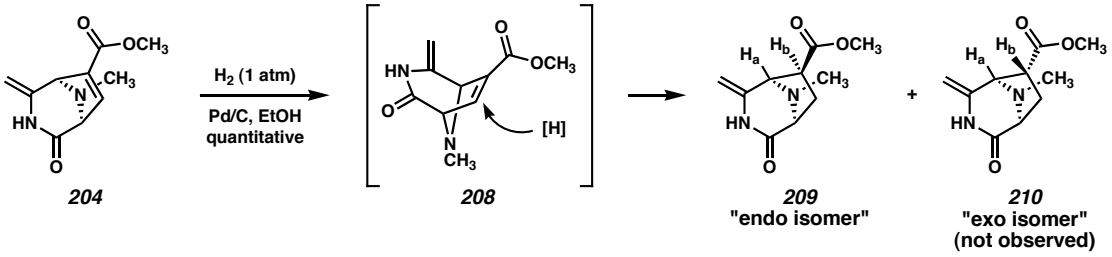
We began our synthetic efforts toward cyanocycline A with the synthesis of an appropriate *N*-methyl dipole precursor. Thus, pyrazinone **145**[7] was alkylated with iodomethane in ethanol to provide oxidopyrazinium salt **207** (Scheme 3.2). Gratifyingly, **207** proved to be an excellent substrate for the dipolar cycloaddition with methyl propiolate, providing diazabicycle **204** in high yield. The significant difference between this reaction and our previous dipolar cycloaddition conditions[4] concerns the amount of base. Since free triethylamine causes the decomposition of methyl propiolate, precisely one equivalent of triethylamine was used to deprotonate oxidopyrazinium **207**. Further, the addition of a small amount of BHT (0.05 equiv) was found to be beneficial, likely due to a buffering effect of the mildly acidic phenol proton.

Scheme 3.2 Dipolar Cycloaddition with Methyl Propiolate



The next challenge of the synthesis was the reduction of diazabicycle **204** to saturated alcohol **211** (Scheme 3.3). This conversion was accomplished through a two-step sequence. First, catalytic hydrogenation of **204** provided saturated ester **209** as a single diastereomer in quantitative yield. The desired diastereomer results from hydrogenation on the convex face of the diazabicycle in transition state **208**, wherein the enamide blocks the top face of the olefin. The relative stereochemistry of the product was determined by ^{1}H NMR. In the desired "endo" product (**209**), the C-H_a and C-H_b bonds are nearly parallel, such that H_a appears in the ^{1}H NMR as a clean doublet. Comparatively, in "exo" compounds such as **210**, the C-H_a and C-H_b bonds are nearly perpendicular, such that H_a is a clear singlet by ^{1}H NMR.[8,9]

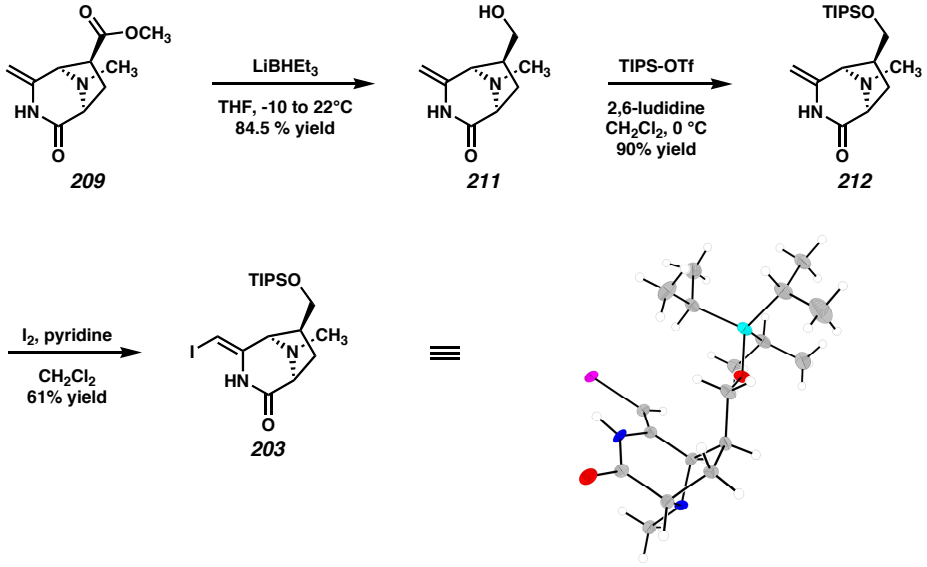
Scheme 3.3 Stereoselective Reduction of the Unsaturated Diazabicycle



We then turned our attention to the reduction of ester **209** to alcohol **211** under conditions that would prevent epimerization of the potentially labile α-stereocenter.[10] This reaction was satisfactorily completed by the treatment of **209** with superhydride, which provided **211** with minimal epimerization (Scheme 3.4). Silylation of the alcohol under standard conditions yielded ether **212**, which was iodinated with molecular iodine to generate iodoenamide **203**. To our delight, iodide **203** was highly crystalline, which

allowed the stereochemistry and olefin geometry of **203** to be proven by X-ray analysis of a single crystal. The crystallographic evidence confirmed the stereochemical assignment of **209** derived from ^{1}H NMR coupling data.

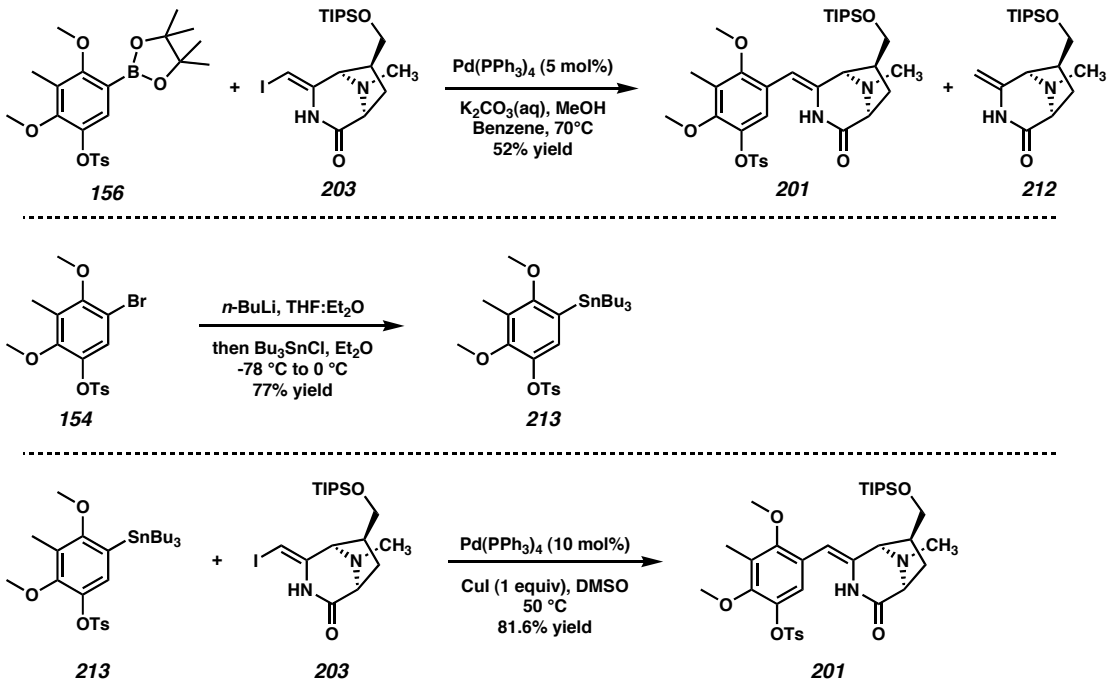
Scheme 3.4 Advancement to the Iodoenamide



The palladium-catalyzed coupling of iodide **203** with arylmetal reagents was then investigated.[11] It was found that Suzuki coupling of the vinyl iodide (**203**) with aryl boronic ester **156** under the conditions optimized for the lemonomycin substrates[4] provided styrene **201** in moderate yield (Scheme 3.5). Unfortunately, this reaction was complicated by competitive reduction of iodide **203** to enamide **212**.

We therefore investigated the potential Stille coupling of **203** to provide **201**. To facilitate this coupling, aryl stannane **213** was synthesized from aryl bromide **154** in good yield. Stille coupling in the presence of copper iodide then cleanly yielded styrene **201** in good yield with only trace amounts of the vinyl iodide reduction product (**212**).[12]

Scheme 3.5 Styrene Synthesis

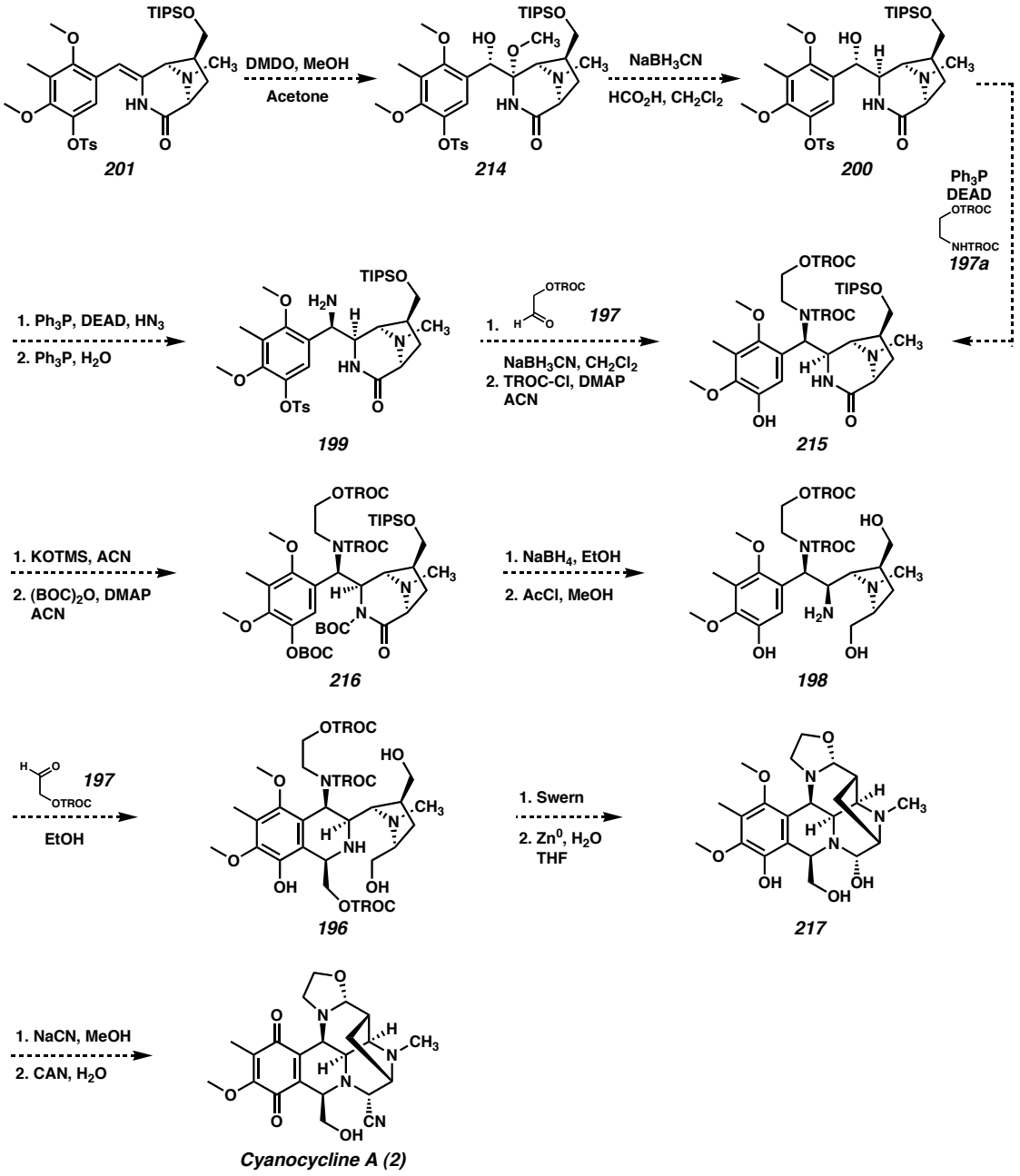


Proposal for Completion of the Silyl Ether Route

We expect that styrene **201** will be amenable to conversion to cyanocycline A (Scheme 3.6). Following the procedure of Fukuyama, we expect that oxidation of styrene **201** with dimethyldioxirane in methanol will yield aminol **214**.[5] Reduction with sodium cyanoborohydride should generate alcohol **200**, which will be advanced to amine **199** by Mitsunobu inversion followed by azide reduction. Reductive amination with aldehyde **197** followed by acylation of the resulting amine will provide protected amino alcohol **215**. Alternatively, **215** may be directly accessible by a Mitsunobu inversion of **200** with carbamate **197a**. Detosylation of the phenol and activation of the lactam with di-*tert*-butyldicarbonate is expected to produce imide **216**, which will be converted to aminotriol **198** by reduction and acidic deprotection. Pictet-Spengler cyclization with aldehyde **197** will synthesize tetrahydroisoquinoline **196**.[13] Swern oxidation followed by zinc mediated

cleavage of the TROC groups should generate oxazolidine **217**, which will be converted to cyanocycline A (**2**) by treatment with sodium cyanide and cerium(IV) oxidation.

Scheme 3.6 Planned Completion of the Silyl Ether Route



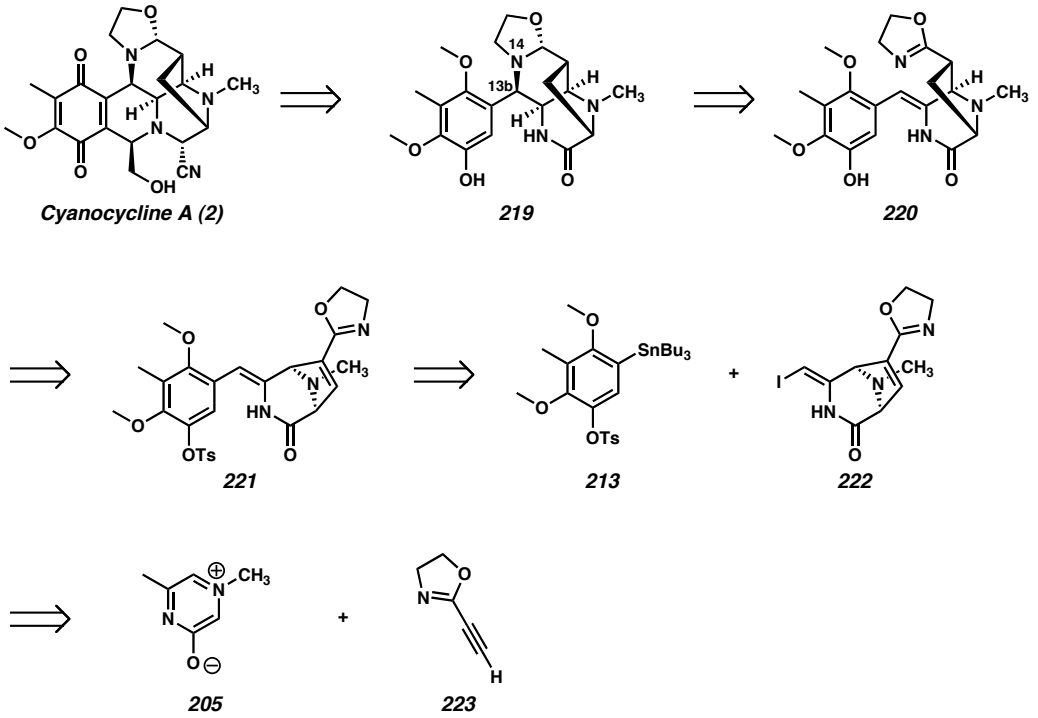
3.2 Second Generation Approach Toward (+)-Cyanocycline A

Retrosynthetic Analysis: Oxazoline Route

Our first generation route toward cyanocycline A is thematically conservative and therefore likely to provide a total synthesis of the natural product. We also wished, however, to approach cyanocycline A from a daring angle that might lead to a more efficient and intellectually valuable synthesis of the natural product. We therefore developed and pursued a second generation synthetic route featuring a proposal for an unprecedented reductive cyclization of an oxazoline with an alkene.

We expected that cyanocycline A (**2**) would be accessible by a glyoxalate Pictet-Spengler cyclization and oxidation state adjustment from lactam **219** (Scheme 3.7). Disconnection of the C(13b)-N(14) bond by retrosynthetic application of our proposed reductive cyclization reaction simplified **219** to oxazoline **220**. Retrosynthetic hydrogenation led to alkene **221**, and a subsequent Stille coupling transform revealed aryl stannane **213** and iodoenamide **222**. We expected to synthesize enamide **222** from dipole **205** and alkynyl oxazoline **223** by a dipolar cycloaddition reaction.

Scheme 3.7 Second Generation Retrosynthesis of Cyanocycline A



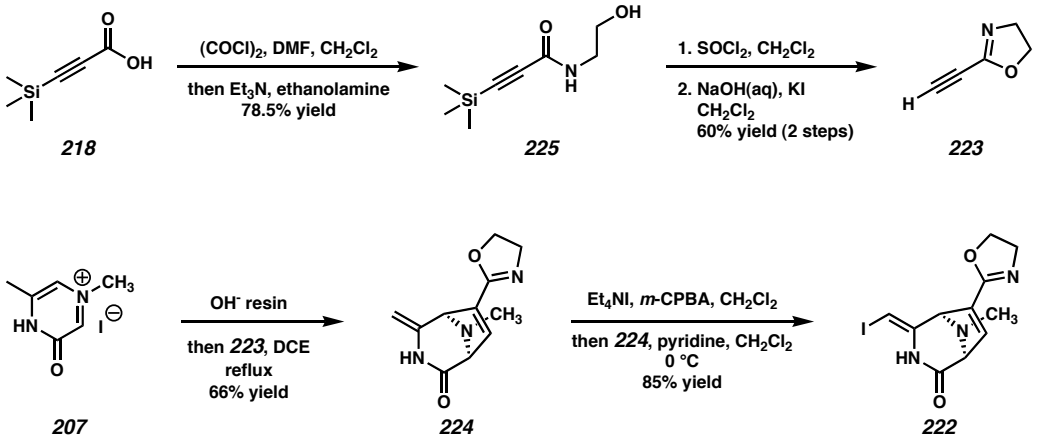
Our second-generation retrosynthesis resolves the differences between lemonomycin and cyanocycline A through reactions both similar to and substantially different from our first generation route. In analogy to our first generation route, the N(5a) methyl group is derived from the *N*-methyl dipole **205**, and the C(4) stereochemistry is again planned to be set by a diastereoselective hydrogenation reaction. Contrastingly, we now plan to address the oxazolidine ring and the C(13b) oxidation state directly by the cyclization of the oxazoline and enamide moieties of **220**.

Synthetic Progress Along the Oxazoline Route

The first challenge of the oxazoline route was the synthesis of alkynyl oxazoline **223** (Scheme 3.8). We began this synthesis with acid **218**, which was smoothly

converted to hydroxyamide **225** via the intermediate acid chloride. Subsequent chlorination with thionyl chloride followed by treatment with sodium hydroxide and potassium iodide cleanly provided alkyne **223**.[14]

Scheme 3.8 Dipolar Cycloaddition with the Alkynyl Oxazoline

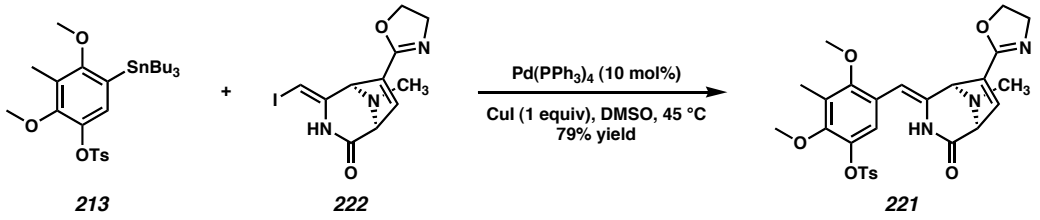


With **223** in hand, we investigated the dipolar cycloaddition with oxidopyrazinium **207**. Unfortunately, the amine-mediated conditions that had proven useful for our earlier substrates provide only low yields (< 46%) of diazabicycle **224**. We therefore turned to a modification of the original conditions reported by Joule,[15] in which oxidopyrazinium **207** is deprotonated with ion exchange resin, isolated as the salt-free dipole (**205**), and then reacted with a dipolarophile. After optimization of these conditions, we found that diazabicycle **224** could be produced in moderate yield by performing the dipolar cycloaddition at elevated temperature in dichloroethane. Despite the moderate yield, this reaction represents a substantial advancement of this type of cycloaddition to the use of a weakly activated acetylenic dipolarophile. Iodination of **224** also proved difficult, but good yields of iodide **222** could be obtained under modified Sha

conditions employing *meta*-chloroperbenzoic acid and tetraethylammonium iodide in pyridine-buffered dichloromethane.[16]

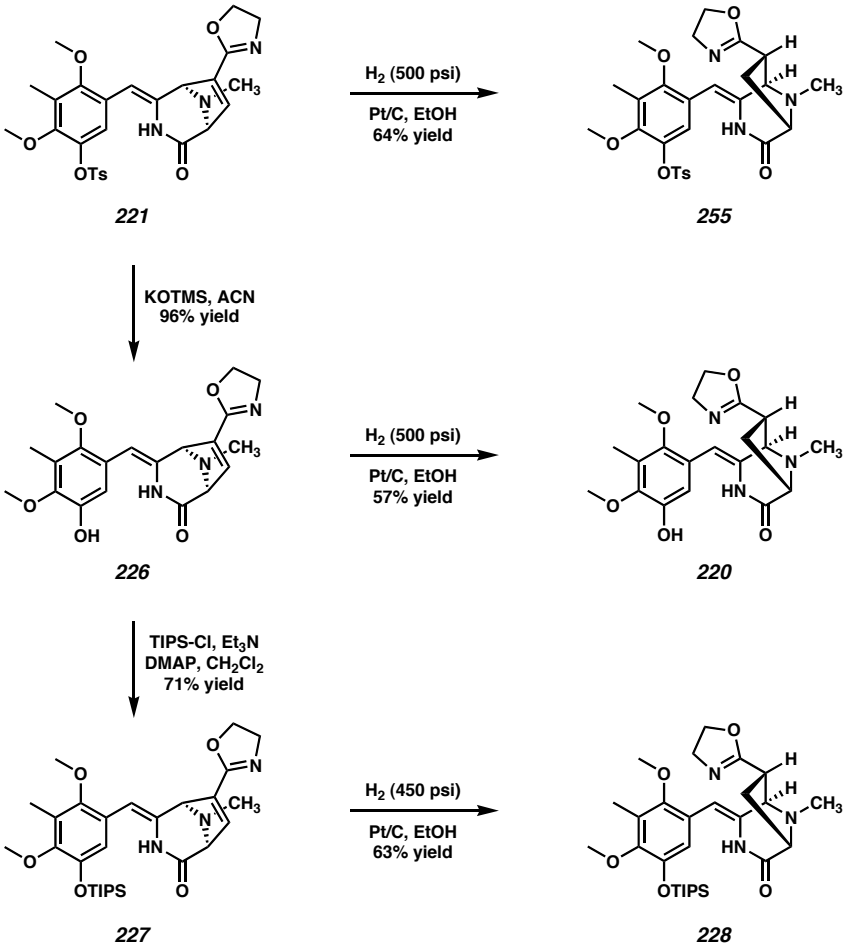
Having developed a synthesis for the diazabicyclic fragment, we investigated the Stille coupling of iodide **222** with stannane **213** (Scheme 3.9).[17] Several simple conditions (Pd(0) source, ligand, solvent) failed to provide the styrene. However, a hit was discovered by application of Corey's cuprous chloride accelerated conditions, which yielded the coupled product (**221**) in 52% yield.[18,12] Further experimentation with copper(I) accelerated conditions led to an optimized protocol that employed stoichiometric cuprous iodide and catalytic tetrakis(triphenylphosphine)palladium(0) in dimethylsulfoxide, which generated styrene **221** in good yield.[19]

Scheme 3.9 Stille Coupling



Styrene **221** was then advanced to three electronically differentiated substrates for the reductive cyclization reaction (Scheme 3.10). Immediate hydrogenation provided oxazoline **255**, while detosylation followed by hydrogenation yielded phenol **220**. Silyl ether **228** was produced by silylation of phenol **226** with triisopropylsilyl chloride followed by catalytic hydrogenation with carbon-supported platinum.[20]

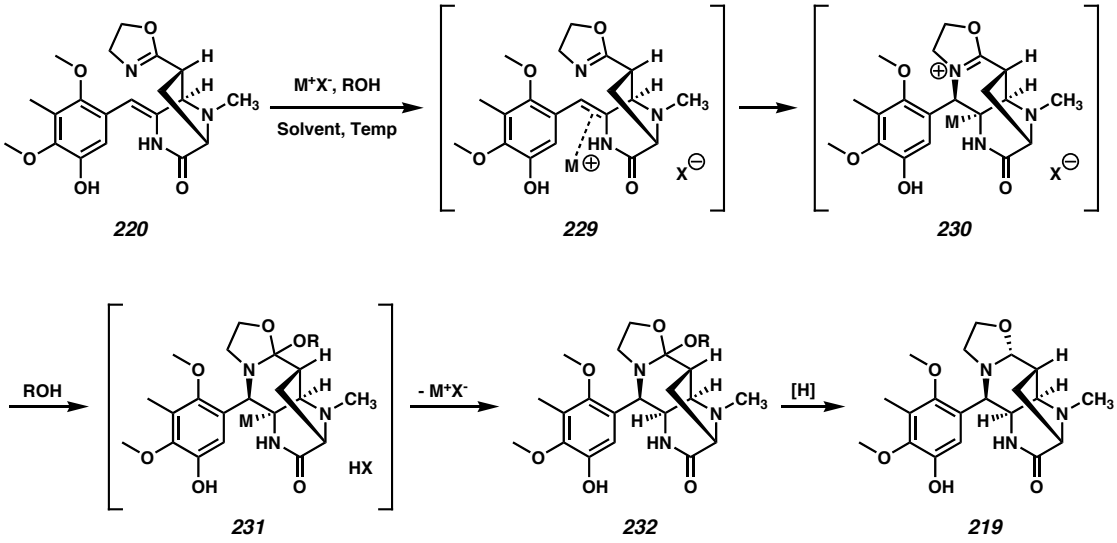
Scheme 3.10 Cyclization Substrate Synthesis



Two strategies toward the desired oxazoline/olefin cyclization have been pursued. The first involved the use of high-oxidation state late transition metal π-acids (Scheme 3.11). It was hoped that activation of the olefin by the metal in intermediate **229** would lead to attack of the oxazoline nitrogen, providing cationic intermediate **230**. Quenching of the cation with an alcohol nucleophile would generate complex **231**, from which protonolysis of the metal-carbon bond would yield piperidine **232** and the regenerated metal catalyst. It was expected that **232** would be amenable to hydride reduction to oxazolidine **219**. Unfortunately, attempts to conduct this reaction with a variety of

platinum(II) and cationic gold(I) catalysts led only to oxazoline hydrolysis and epimerization of the C(4) stereocenter.

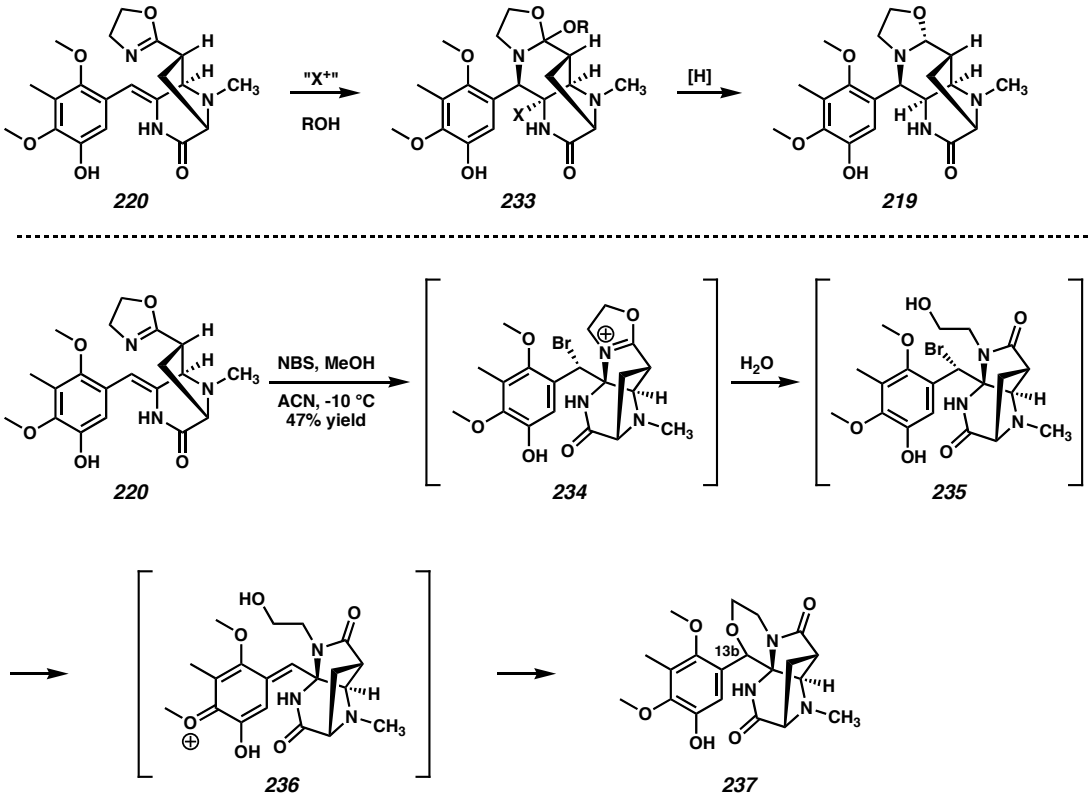
Scheme 3.11 Proposed Cyclization by π-Acid Activation



We then turned to oxidation of olefin **220** with halogenation reagents (Scheme 3.12). It was hoped that activation of **220** by a halogen source in the presence of an alcohol nucleophile would lead to piperidine **233** through a mechanism similar to that shown in Scheme 3.11. It was then expected that reduction of **233** with an appropriate hydride source would remove both the halide and the alkoxide substituents to yield oxazolidine **219**. In attempting this reaction, we quickly discovered that *N*-bromosuccinimide was uniquely effective for the oxidation of **220**. However, the isolated product proved to be pyrrolidinone **237** rather than the desired piperidine (**233**). Although the mechanism of this oxidative cyclization reaction has not been studied, we propose that pyrrolidine **237** results from bromonium-mediated 5-exo cyclization of

oxazoline **220** to cationic intermediate **234**. Rapid hydrolysis of **234** by adventitious water provides hydroxyamide **235**. Loss of bromide forms quinone-methide cation **236**, which is attacked by the hydroxyl group to generate the morpholine ring. Hydroxyamide **235** could alternatively undergo S_N2 displacement of the bromide to yield **237** directly.[21]

Scheme 3.12 *N*-Bromosuccinimide Mediated Cyclization



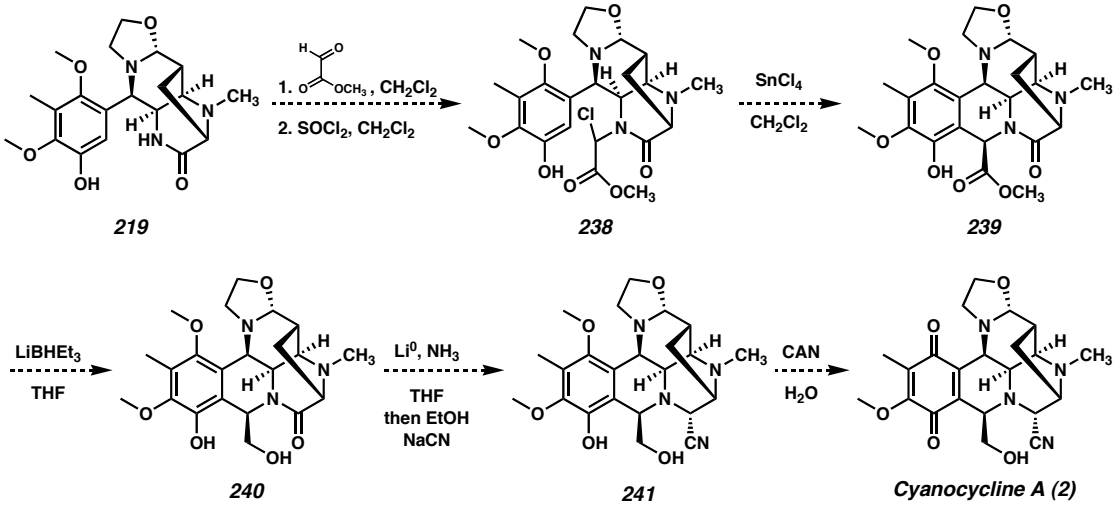
The structure of **237** was assigned on the basis of the NMR resonances of the benzylic carbon and attached proton, the HETCOR correlation of these two resonances, and the resonance of the aminal carbon. The ^{1}H NMR exhibits a sharp singlet at 5.43 ppm that is assigned as the benzylic proton attached to C(13b). A HETCOR spectrum[22] shows a correlation between this proton and a carbon at 73.6 ppm, which indicates an

attached oxygen atom rather than an attached nitrogen atom. A second carbon resonance appears at 72.9 ppm, which is in good agreement with the value expected for an aminal carbon. The stereochemistry of the aminal is enforced by the caged ring structure. The benzylic stereochemistry has not been determined.

Proposal for Completion of the Oxazoline Route

While our early investigations into the conversion of oxazoline **220** to piperidine **219** have not been successful, we anticipate that this reaction will eventually be accomplished by radical reduction, an oxidation-reduction sequence, or photolysis in the presence of a hydrogen atom donor. With **219** in hand, we expect that condensation with methyl glyoxalate followed by treatment with thionyl chloride will yield α-chloroamide **238** (Scheme 3.13). Tin(IV) mediated chloride elimination will then trigger an iminium ion cyclization, producing tetrahydroisoquinoline **239**.[23] Reduction under non-Lewis acidic conditions should provide alcohol **240** without reducing the oxazolidine ring. Dissolving metal conditions will reduce the amide to the carbinolamine, which will be trapped as aminonitrile **241**.[23] The natural product will then arise by cerium(IV) oxidation of the phenol.

Scheme 3.13 Proposed Completion of the Oxazoline Route



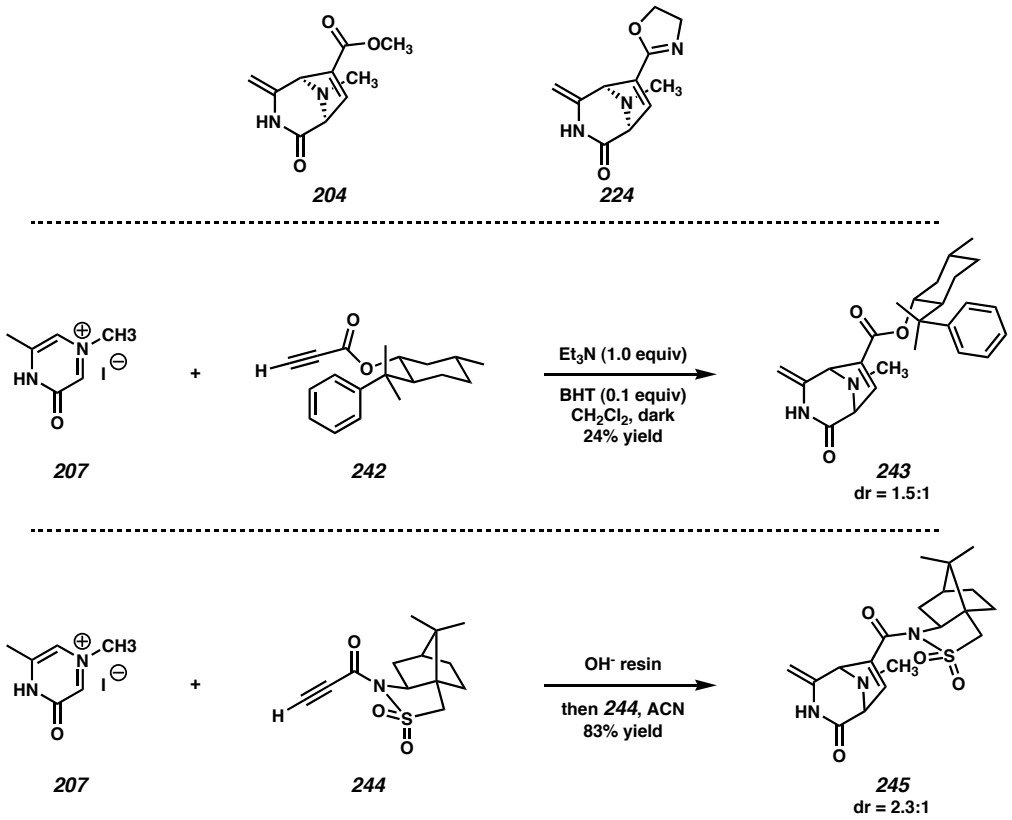
3.3 Progress Toward an Asymmetric Alkyne Dipolar Cycloaddition

Known Chiral Auxiliaries

Our proposed and partially executed syntheses of cyanocycline A utilize a series of diastereoselective reactions, such that all of the stereocenters in the natural product will be set from the stereocenters extant in the early diazabicyclic intermediates (**204** and **224**). Further, it is likely that an ester-appended diazabicycle such as **204** could be readily converted to oxazoline **224**. To render either synthetic route asymmetric, access to an enantiopure ester-appended diazabicycle is required. Such an enantiopure diazabicycle could arise by the dipolar cycloaddition of oxidopyrazinium **207** with an appropriate acylated chiral auxiliary (Scheme 3.14). In this regard, we investigated the dipolar cycloaddition of **207** with the alkynoate of 8-phenylmenthol (**242**)[24] and the alkynamide of Oppolzer's Sultam (**244**).[25] The phenylmenthol-derived alkynoate provided a poor yield of inseparable cycloadducts as a nearly even mixture of diastereomers. The Oppolzer's Sultam-derived alkynamide faired somewhat better,

providing cycloadducts **245** in good yield, but the selectivity is still well below the synthetically useful threshold.[26]

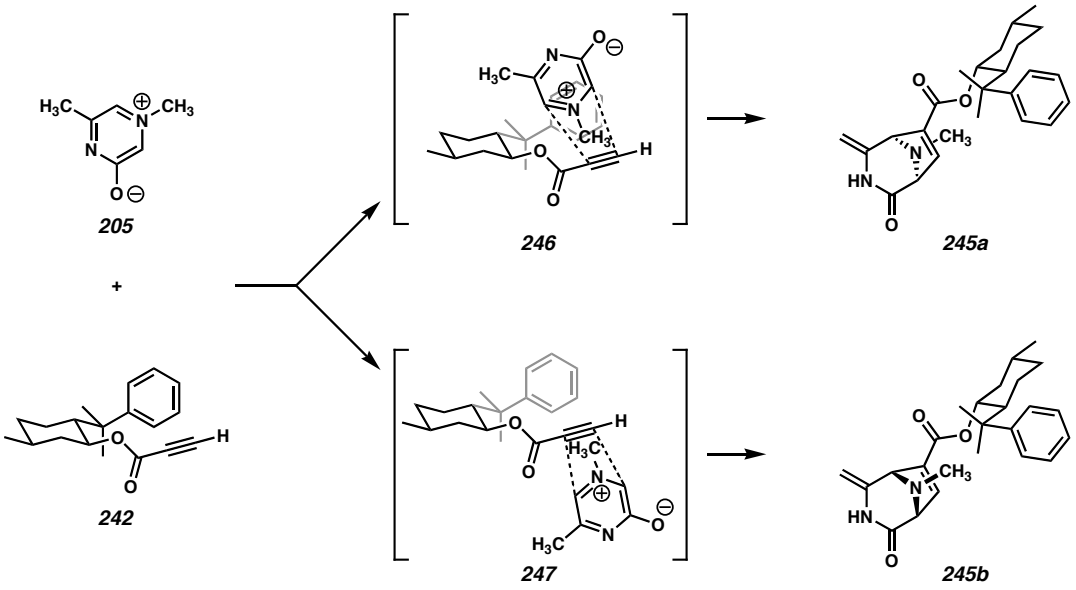
Scheme 3.14 Dipolar Cycloaddition with Known Chiral Auxiliaries



The poor diastereoselectivity of these reactions was initially surprising. The pheylmenthol auxiliary in particular should provide excellent facial bias around the alkyne, allowing the dipole to approach only opposite the phenyl ring (Scheme 3.15). It was soon realized, however, that facial bias around the alkyne is insufficient for diastereoselectivity. For example, reaction of dipole **205** with alkynoate **242** can proceed through transition states **246** and **247**, which both involve approach of the dipole away from the auxiliary's phenyl ring, but which provide opposite diastereomers of product

(**245a** vs. **245b**). To impart diastereocontrol, the auxiliary must therefore control both the facial bias of the alkyne and the orientation of the approaching dipole, differentiating the "endo" approach (e.g., **246**) from the "exo" approach (e.g., **247**).[27]

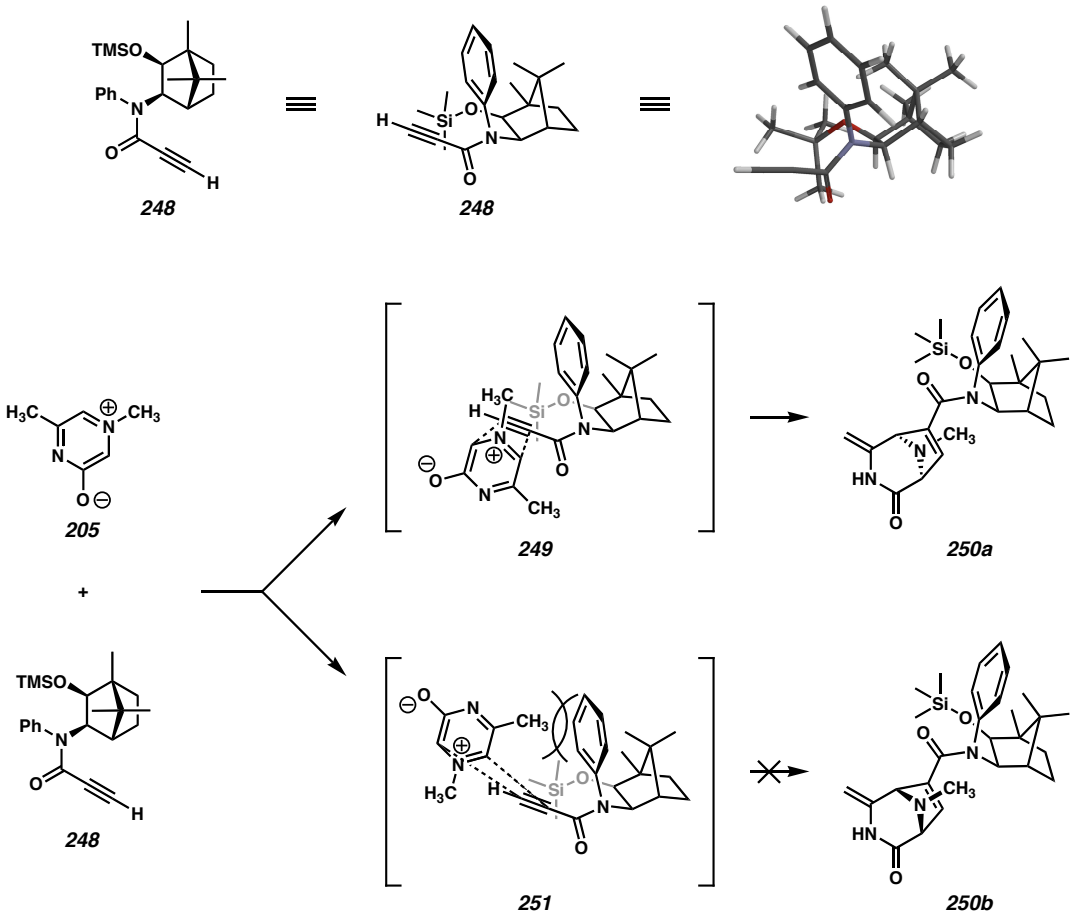
Scheme 3.15 Dipolar Cycloaddition with the Phenylmenthol-derived Auxiliary



Design and Utilization of a New Chiral Auxiliary

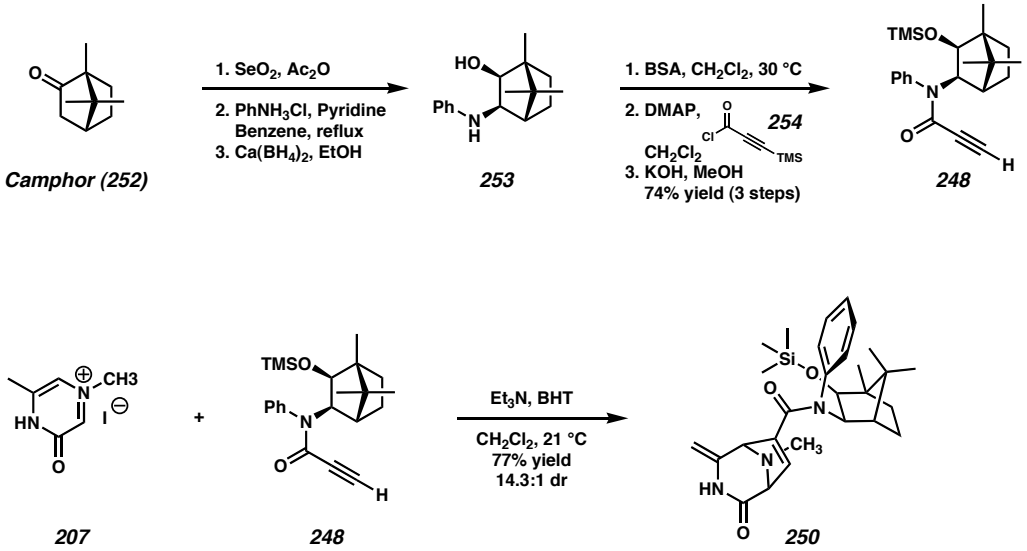
To distinguish the endo and exo orientations of the dipole, auxiliary **248** was designed (Scheme 3.16).[28] In its lowest energy conformation,[29] the phenyl ring of **248** is oriented perpendicularly to the reactive alkyne. This orientation places the steric bulk of the phenyl ring above the alkynoate, while the silyloxy group blocks the back face. Dipole **205** must therefore approach over the front face. In exo transition state **249**, the dipole's *N*-methyl group is accommodated by the auxiliary's phenyl ring. In endo transition state **251**, the phenyl group and the dipole's *C*-methyl group clash extensively, destabilizing this pathway.

Scheme 3.16 Design of a New Chiral Auxiliary



Kevin Allan synthesized the desired alkynoate **248** from camphor (Scheme 3.17). Camphor (**252**) was advanced by known procedures[30] to amino alcohol **253**, which was selectively *O*-silylated with *N*,*O*-bis(trimethysilyl)acetamide. Acylation and alkyne deprotection afforded alkynoate **248**. This alkynoate was then reacted with oxidopyrazinium **207** and triethylamine in dichloromethane to provide cycloadduct **250** with a diastereomeric ratio of 14.3 to 1. Although the relative stereochemistry of **250** has not been confirmed, this reaction represents a major advance in alkyne dipolar cycloaddition chemistry that will lead to an asymmetric synthesis of cyanocycline A.

Scheme 3.17 Synthesis and Utilization of the New Auxiliary



3.4 Conclusion

Substantial progress toward the synthesis of (+)-cyanocycline A has been completed along two synthetic routes. Progress along the silyl ether route led to the discovery of a new diastereoselective hydrogenation of an unsaturated diazabicyclic intermediate to set the C(4) stereochemistry of cyanocycline A. The product of this reduction was advanced through a convergent Stille coupling reaction. The coupled intermediate contains all but six of the heavy atoms of cyanocycline A with the correct stereochemistry at each of the stereogenic carbons. Further, the enamide functionality is an ideal precursor for installation of the C(13b) amino group.

Progress along the oxazoline route has led to the development of a novel dipolar cycloaddition of an alkynyl oxazoline. The resulting diazabicycle was advanced through a convergent Stille coupling reaction and diastereoselective hydrogenation to a late stage intermediate for the synthesis of cyanocycline A. This intermediate contains all but three

of the heavy atoms of cyanocycline A and has the correct relative stereochemistry for advancement to the natural product. Attempted cyclization of this intermediate has not yet been fully successful, although a compound with the correct C(13b) oxidation state was formed by reaction with *N*-bromosuccinimide.

In collaboration with Kevin Allan, a novel chiral auxiliary for the alkynoate dipolar cycloaddition was designed and synthesized. Application of the chiral auxiliary led to the production of cycloadducts with 20:1 diastereoselectivity. It is expected that the major cycloadduct will be readily converted to intermediates in either of our synthetic routes. Advancement of that material eventually will provide an asymmetric synthesis of (+)-cyanocycline A.

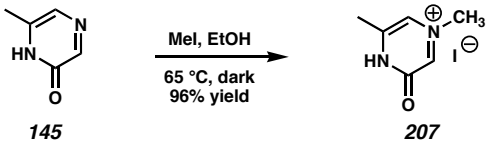
3.5 Experimental Procedures

Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 22 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Acrolein was distilled under nitrogen immediately prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, anisaldehyde, permanganate, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Mercury 500 (at 500 MHz and 125 MHz respectively), or a Varian Mercury 600 (600 MHz for proton only) spectrometer and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). UV spectra were measured on a Beckman-Coulter DU 7400 spectrophotometer. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies

can be obtained on request, free of charge, by quoting the publication citation and the deposition number (see individual structures for deposition number).

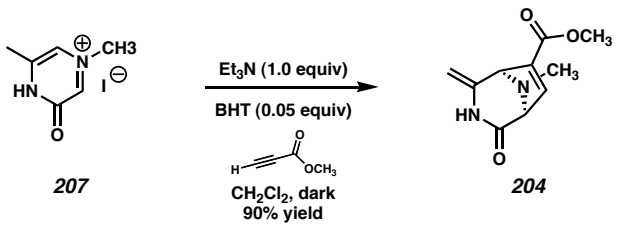
Preparation of Compounds



145 *207*

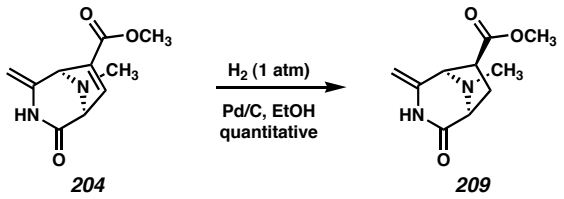
Oxidopyrazinium 207

(Note: the reaction was performed in a foil-wrapped flask equipped with a reflux condenser.) To a suspension of pyrazinone **145** (5.0 g, 45.4 mmol) in anhydrous ethanol (90 mL) was added iodomethane (14.1 mL, 227 mmol). The reaction mixture was degassed by cooling to –78 °C and evacuating to 1 torr for 20 min, then flushing with argon. The mixture was then heated to 65 °C. After 27 h, additional iodomethane (7.05 mL, 113.5 mmol) was added. After 47 h, the reaction was cooled to 0 °C and filtered. The filter cake was washed with cold (0 °C) ethanol (100 mL) and dried under vacuum to yield oxidopyrazinium **207** (11.0 g, 96% yield) as a red-orange powder: ^{1}H NMR (300 MHz, D_2O) δ 8.38 (s, 1H), 7.59 (s, 1H), 4.24 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 158.2, 149.4, 142.0, 118.6, 49.3, 16.9; IR (Nujol) 1685, 1635, 1462 cm^{-1}; Elemental Analysis $C_6H_9N_2OI$, calc'd: C, 28.59; H, 3.60; N, 11.11; I, 50.35, found, C, 28.66; H, 3.79; N, 10.90; I, 50.68.



Diazbicycle 204

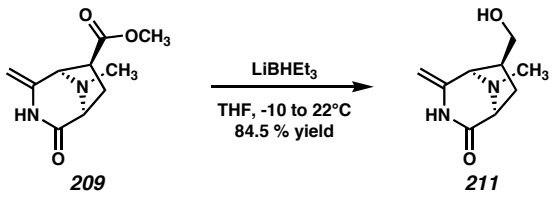
(Note: the reaction was performed in a foil-wrapped flask.) To a suspension of **207** (504 mg, 2.0 mmol) in dichloromethane (6.7 mL) were added BHT (22.0 mg, 100 μmol) and triethylamine (279 μL, 2.0 mmol). After 30 min, methyl propiolate (534 μL, 6.0 mmol) was added. After 5 h 45 min, the mixture was diluted with saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bisulfite (5 mL) and extracted into dichloromethane (2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50:1 to 80:20:1 ethyl acetate:hexanes:triethylamine) to yield **204** (377 mg, 90% yield): R_F 0.37 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.10 (d, J = 2.7 Hz, 1H), 4.42 (s, 1H), 4.33-4.28 (comp m, 2H), 3.96 (s, 1H), 3.78 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.0, 141.3, 138.7, 136.9, 94.0, 71.0, 66.5, 52.1, 36.6; IR (NaCl/film) 3211, 2951, 1721, 1689, 1299, 1256, 1089 cm^{-1}; HRMS (FAB+) calc'd for $[C_{10}H_{12}N_2O_3]^{\bullet+}$: *m/z* 208.0848, found 208.0851.



204 *209*

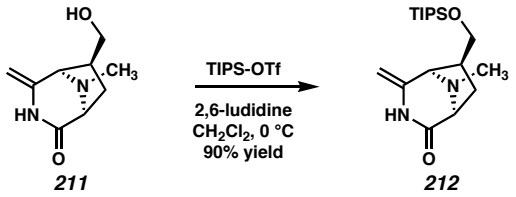
Ester 209

To a solution of **204** (100.0 mg, 480.3 μmol) in ethanol (4.8 mL) was added palladium on carbon (10% w/w, 20 mg). The reaction vessel was purged, flushed with hydrogen, and maintained under 1 atm of hydrogen for 1 h 15 min. The mixture was then filtered directly through a column packed with celite over silica gel (95:5:1 ethyl acetate:ethanol:triethylamine eluent) to provide **209** (100.9 mg, quantitative), which was sufficiently pure for use in the next reaction. An analytically pure sample of **204** was prepared by flash chromatography on silica gel (0:100:1 to 3:97:1 methanol:ethyl acetate: ethyldimethylamine eluent): R_F 0.24 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 4.32 (s, 1H), 4.08 (s, 1H), 3.86 (d, *J* = 6.6 Hz, 1H), 3.65 (s, 3H), 3.48 (d, *J* = 7.2 Hz, 1H), 3.47-3.41 (m, 1H), 2.51-2.33 (comp m, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.9, 138.8, 93.2, 65.3, 65.0, 52.3, 48.0, 35.7, 31.4; IR (NaCl/film) 3199, 2951, 1740, 1690, 1653, 1322, 1205, 1018, 846 cm^{-1}; HRMS (FAB+) calc'd for $[C_{10}H_{14}N_2O_3]^{\bullet+}$: *m/z* 210.1005, found 210.1010.



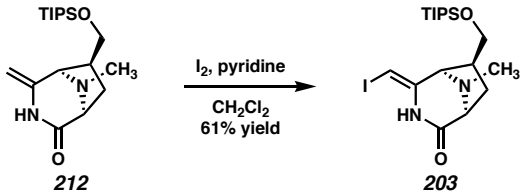
Alcohol 211

To a –10 °C solution of **209** (56 mg, 266 μmol) in tetrahydrofuran (2.7 mL) was added a solution of lithium triethylborohydride in tetrahydrofuran (1 M, 1.33 mL, 1.33 mmol) dropwise over 2 min. After 15 min, the reaction mixture was allowed to warm to 22 °C. After an additional 30 min, the reaction was quenched with ethyl acetate (1 mL). After an additional 5 min, the solution was concentrated and purified by flash chromatography on silica gel (4:96:1 to 13:87:1 methanol:ethyl acetate:triethylamine eluent) to yield **211** (41.0 mg, 84.5% yield): R_F 0.12 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 4.42 (s, 1H), 4.21 (s, 1H), 3.69 (d, *J* = 6.3 Hz, 1H), 3.58 (d, *J* = 7.5 Hz, 2H), 3.43 (d, *J* = 7.5 Hz, 1H), 2.78-2.66 (m, 1H), 2.50-2.38 (m, 1H), 2.45 (s, 3H) 2.36 (br s, 1H), 1.51 (dd, *J* = 13.2, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 139.2, 93.2, 64.7, 64.6, 63.5, 43.3, 35.6, 32.7; IR (NaCl/film) 3321 br, 3202, 2944, 1682, 1322, 1044 cm^{-1}; HRMS (EI+) calc'd for $[C_9H_{14}N_2O_2]^{\bullet+}$: *m/z* 182.1055, found 182.1059.



Silyl Ether 212

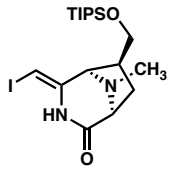
To a 0 °C solution of alcohol **211** (108.2 mg, 593.7 μmol) in dichloromethane (6.0 mL) were added 2,6-lutidine (242.0 μL, 2.08 mmol) and triisopropylsilyl trifluoromethanesulfonate (478.7 μL, 1.78 mmol). After 20 min, the reaction mixture was diluted with ethyl acetate (75 mL) and washed with water (75 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (55:45:1 to 6:35:1 ethyl acetate:hexanes:ethyldimethylamine eluent) to provide silyl ether **212** (181.0 mg, 90% yield): R_F 0.38 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 4.39 (s, 1H), 4.20 (s, 1H), 3.69 (d, *J* = 6.0 Hz, 1H), 3.62 (d, *J* = 7.8 Hz, 2H), 3.44 (d, *J* = 7.5 Hz, 1H), 2.74-2.62 (m, 1H), 2.47 (s, 3H), 2.46-2.36 (m, 1H), 1.50 (dd, *J* = 13.2, 6.0 Hz, 1H), 1.08-0.98 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 138.4, 93.8, 64.9, 64.6, 64.0, 44.1, 35.6, 32.5, 18.2, 12.1; IR (NaCl/film) 2942, 2865, 1689, 1099, 882, 681 cm^{-1}; HRMS (FAB+) calc'd for $[C_{18}H_{34}N_2O_2Si+H]^+$: *m/z* 339.2468, found 339.2462.



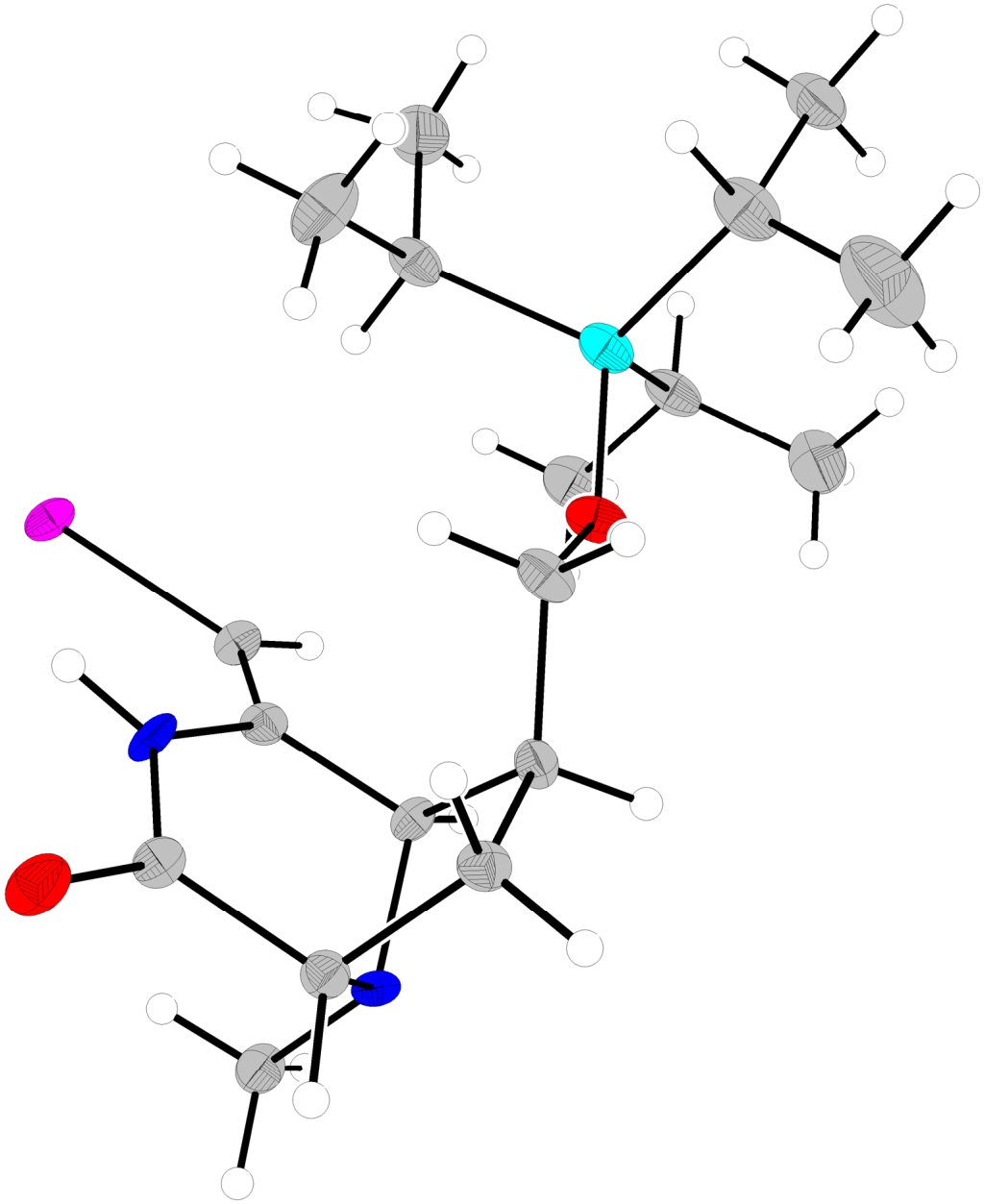
Iodoenamide 203

(Note: the reaction was performed in a foil-wrapped flask.) To a solution of enamide **212** (181.0 mg, 534.6 μmol) in dichloromethane (5.3 mL) were added pyridine (130 μL, 1.60 mmol) and iodine (149.2 mg, 588.0 μmol). After 15 min, the reaction mixture was diluted with ethyl acetate (75 mL) and washed with a mixture of water (100 mL) and saturated aqueous sodium thiosulfate (5 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80:1 to 30:70:1 ethyl acetate:hexanes:ethyldimethlamine eluent) to provide iodide **203** (152.0 mg, 61% yield): R_F 0.77 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (br s, 1H), 5.11 (s, 1H), 3.91 (d, *J* = 6.3 Hz, 1H), 3.64 (dd, *J* = 10.2 6.0 Hz, 1H), 3.45 (app t, *J* = 10.2 Hz, 1H), 3.45 (d, *J* = 7.5 Hz, 1H), 2.73-2.61 (m, 1H), 2.47-2.35 (m, 1H), 2.43 (s, 3H), 1.43 (dd, *J* = 13.2, 5.7 Hz, 1H), 1.06-1.01 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 140.1, 66.7, 65.0, 63.7, 55.1, 44.4, 35.7, 31.8, 18.3, 12.1; IR (NaCl/film) 3217, 2940, 2865, 1700, 1634, 1299, 1109, 1092, 691 cm^{-1}; HRMS (FAB+) calc'd for $[C_{18}H_{33}N_2O_2SiI+H]^+$: *m/z* 465.1435, found 465.1445. A crystal of sufficient quality for X-ray analysis was grown from ethyl acetate:hexanes by slow diffusion.

Crystal Structure of 203



203



Crystal data and structure refinement for 203 (CCDC 286418).

Empirical formula	$C_{18}H_{33}IN_2O_2Si$
Formula weight	464.45
Crystallization Solvent	Ethyl acetate/hexanes
Crystal Habit	Plate
Crystal size	0.26 x 0.18 x 0.01 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 8013 reflections used		
in lattice determination	2.88 to 29.24°	
Unit cell dimensions	a = 7.4435(5) Å	α= 89.566(4)°
	b = 8.1736(6) Å	β= 81.264(4)°
	c = 19.5349(14) Å	γ = 65.225(3)°
Volume	1064.51(13) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.449 Mg/m^3	
F(000)	476	
Data collection program	Bruker SMART v5.630	
θ range for data collection	2.11 to 30.48°	
Completeness to θ = 30.48°	87.5 %	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-26 \le l \le 27$	
Data collection scan type	ω scans at 7 ϕ settings	

Data reduction program	Bruker SAINT v6.45A
Reflections collected	21316
Independent reflections	5678 [R_{int}= 0.0847]
Absorption coefficient	1.573 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9844 and 0.6852

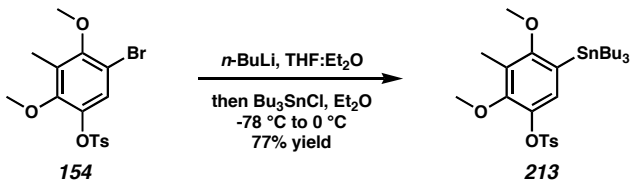
Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5678 / 0 / 224
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.656
Final R indices [I>2σ(I), 4244 reflections]	R1 = 0.0666, *w*R2 = 0.0849
R indices (all data)	R1 = 0.0972, *w*R2 = 0.0874
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	1.920 and -3.266 e.$Å^{-3}$

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

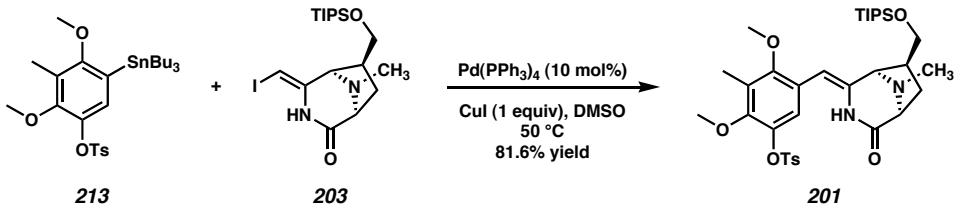
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



154 *213*

Stannane 213

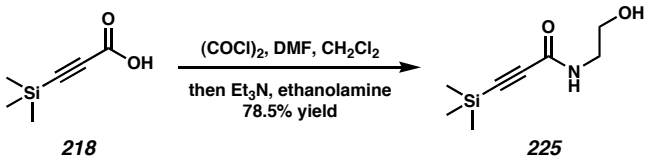
To a –78 °C solution of bromide **154** (1.0 g, 2.5 mmol) in tetrahydrofuran:diethyl ether (1:1, 25 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 1.1 mL, 2.75 mmol) dropwise down the flask walls over 45 sec. After 15 min, a –78 °C solution of tributyltin chloride (814 μL, 3.0 mmol) in diethyl ether (6.0 mL) was added via cannula. After an additional 10 min, the reaction mixture was warmed to 0 °C over 10 min, then quenched with water (100 mL). The mixture was extracted into diethyl ether (2 x 25 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (5:95 to 10:90 ethyl acetate:hexanes eluent) to provide stannane **213** (1.17 g, 77% yield): R_F 0.55 (15:85 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.30 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 2H), 3.56 (s, 3H), 3.35 (s, 3H), 2.06 (s, 3H), 1.83 (s, 3H), 1.68-1.55 (comp m, 6H), 1.44-1.31 (comp m, 6H), 1.14-1.07 (comp m, 6H), 0.93 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 163.7, 153.4, 144.9, 140.6, 135.0, 130.0, 129.5, 129.0, 125.7, 100.7, 61.2, 60.9, 29.9, 28.1, 21.6, 14.3, 11.0, 10.8; IR (NaCl/film) 2955, 2926, 1465, 1378, 1188, 1178, 1095, 1010, 988, 825, 812 cm^{-1}; HRMS (FAB+) calc'd for $[C_{28}H_{44}O_5SSn+H]^+$: *m/z* 613.2010, found 613.2023.



Styrene 201

(Note: the reaction was performed in a foil-wrapped vessel.) To a solution of **213** (78.9 mg, 129 μmol) and **203** (30.0 mg, 64.5 μmol) in dimethylsulfoxide were added copper(I) iodide (12.3 mg, 64.5 μmol) and tetrakis(triphenylphosphine)palladium(0) (7.5 mg, 6.45 μmol). The reaction mixture was deoxygenated by twice freezing under vacuum and melting under argon. The reaction mixture was then sealed under argon and heated to 50 °C. After 3 h, the mixture was cooled to 22 °C, diluted with ethyl acetate (50 mL), and washed with a mixture of water (135 mL) and saturated aqueous ammonium hydroxide (15 mL) followed by water (150 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:25:50:0.5 to 30:30:40:0.5 ethyl acetate:dichloromethane:hexanes:ethyldimethylamine eluent) to provide styrene **201** (34.7 mg, 81.6% yield): R_F 0.35 (35:35:40 ethyl acetate: dichloromethane:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 5.35 (s, 1H), 3.74 (d, *J* = 6.3 Hz, 1H), 3.69 (s, 3H), 3.68-3.66 (comp m, 2H), 3.65 (s, 3H), 3.50 (d, *J* = 7.8 Hz, 1H), 2.84-2.70 (m, 1H), 2.55-2.43 (m, 1H), 2.50 (s, 3H), 2.46 (s, 3H), 2.15 (s, 3H), 1.54 (dd, *J* = 13.5, 5.7 Hz, 1H), 1.04-0.99 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 153.9, 145.5, 139.2, 133.5, 129.9, 128.5, 127.6, 123.7, 122.3, 103.4, 66.3, 65.0, 64.3, 61.1, 60.4,

45.1, 35.7, 32.7, 22.0, 18.2,, 12.1, 10.0; IR (NaCl/film) 2942, 2865, 1693, 1377, 1191, 1178, 1111, 992 cm^{-1}; HRMS (FAB+) calc'd for $[C_{34}H_{50}N_2O_7SSi+H]^+$: *m/z* 659.3186, found 659.3209.

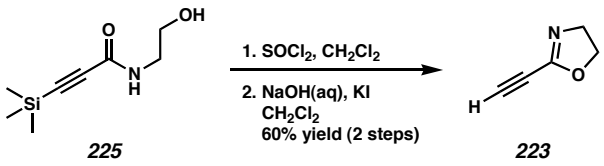


218 ***225***

Amide 225

To a solution of acid **218** (9.5 g, 66.8 mmol) and dimethylformamide (517 μL, 6.68 mmol) in dichloromethane (267 mL) was added oxalyl chloride (6.41 mL, 73.5 mmol) dropwise over 10 min (caution: gas evolution). After 1.5 h, this reaction mixture was added dropwise over 20 min to a solution of ethanolamine (12.1 mL, 200.4 mmol) and triethylamine (18.6 mL, 133.6 mmol) in dichloromethane (200 mL) (caution: exotherm). After an additional 2 h 10 min, the resulting reaction mixture was quenched into aqueous hydrochloric acid (0.5 M, 600 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 80:20 ethyl acetate:hexanes eluent) to provide amide **225** (9.72 g, 78.5% yield): R_F 0.31 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br s, 1H), 3.73 (app t, *J* = 5.4 Hz, 2H), 3.44 (app q, *J* = 5.4 Hz, 2H), 2.99 (br s, 1H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 97.5, 92.4, 61.6, 42.6, -0.6; IR (NaCl/film)

3270 br, 3057, 2960, 1632, 1546, 1251, 846 cm^{-1}; HRMS (EI+) calc'd for $[C_8H_{15}NO_2Si]^{\bullet+}$: *m/z* 185.0872, found 185.0877.



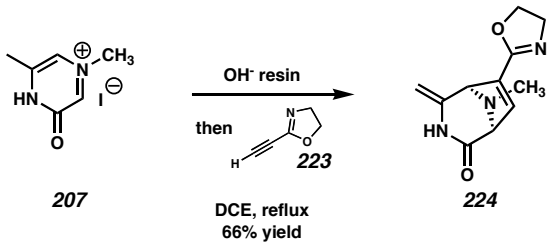
225 ***223***

Oxazoline 223

To a 0 °C solution of amide **225** (9.72 g, 52.46 mmol) in dichloromethane (75 mL) was added thionyl chloride (11.5 mL, 157.38 mmol) dropwise over 5 min. The reaction mixture was then allowed to warm to 23 °C for 8 h, after which water (500 mL) was added (caution: gas evolution). The phases were separated, and the organics were washed with a mixture of water (100 mL) and saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 25:75 ethyl acetate:hexanes eluent) to provide the alkyl chloride (8.83 g, 83% yield).

To a solution of the chloride (8.83 g, 43.35 mmol) in dichloromethane (87 mL) were added aqueous sodium hydroxide (1 M, 217 mL, 217 mmol) and potassium iodide (3.60 g, 21.68 mmol). The reaction mixture was stirred vigorously for 5.5 h. The mixture was then diluted with saturated aqueous sodium chloride (250 mL) and extracted into dichloromethane (2 x 75 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (35:65 to 70:30 diethyl ether:pentane eluent) to provide oxazoline **223** (2.95 g, 72% yield) as a volatile white solid that must be stored below –20 °C to prevent decomposition and sublimation:

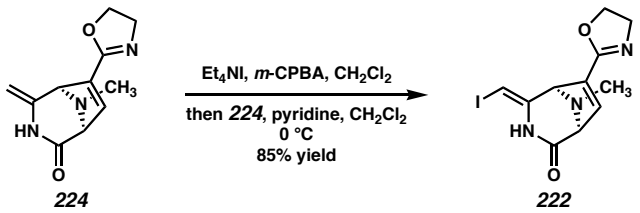
R_F 0.15 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 3.61 (t, *J* = 9.9 Hz, 2H), 3.38 (t, *J* = 9.9 Hz, 2H), 2.67 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 149.7, 78.7, 73.1, 67.6, 55.4; IR (NaCl/film) 3273, 3232, 2128, 1630, 1218, 991, 956, 910, 698 cm^{-1}; HRMS (EI+) calc'd for $[C_5H_5NO]^{\bullet+}$: *m/z* 95.0371, found 95.0368.



Diazabicycle 224

An aqueous solution of **207** (126 mg, 500 μmol) was eluted through a column of Amberlite IRA 400 hydroxide resin (3.95 g, 15 mmol) with 1:1 methanol:water. The UV-active fractions that eluted were collected and concentrated in vacuo. To the resulting semisolid was added a solution of oxazoline **223** (95 mg, 1.0 mmol) in dichloroethane (5 mL). The reaction mixture was heated to reflux for 1 h 15 min, then cooled to 23 °C, diluted with water (55 mL) and saturated aqueous sodium chloride (15 mL), and extracted with dichloromethane (2 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:4:76 to 20:10:70 ethyl acetate:methanol:chloroform eluent) to yield diazabicycle **224** (72.2 mg, 66% yield): R_F 0.30 (10:10:80 ethyl acetate:methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.44 (d, *J* = 1.5 Hz, 1H), 4.41 (d, *J* = 1.5 Hz, 1H), 4.35-4.24 (comp m, 3H), 4.04-3.94 (comp m, 3H), 2.46 (s,

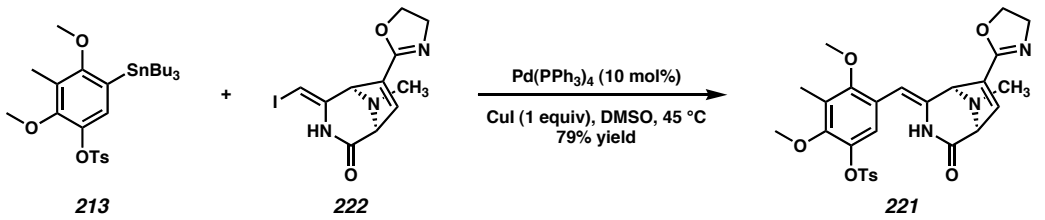
3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.0, 137.5, 136.1, 135.1, 93.4, 71.4, 67.8, 67.5, 55.3, 37.1; IR (NaCl/film) 3203, 2977, 2946, 2904, 2873, 1687, 1656, 1290, 1052 cm^{-1}; HRMS (FAB+) calc'd for $[C_{11}H_{13}N_3O_2]^{\bullet+}$: *m/z* 219.1008, found 219.1002.



Iodoenamide 222

To a 0 °C suspension of tetraethylammonium iodide (1.04 g, 4.05 mmol) in dichloromethane (27 mL) was added *meta*-chloroperbenzoic acid (466 mg, 2.70 mmol). After 25 min, the resulting dark orange solution was added via cannula to a 0 °C solution of **224** (295 mg, 1.35 mmol) and pyridine (546 μL, 6.75 mmol) in dichloromethane (9.0 mL). After an additional 10 min, the reaction mixture was poured into saturated aqueous sodium bicarbonate (75 mL), and the remaining iodination reagent was quenched by the dropwise addition of saturated aqueous sodium thiosulfate (5 mL) until the red color dissipated. The phases were separated, and the aqueous layer was extracted with dichloromethane (25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:20:80:1 to 2:18:80:1 methanol:ethyl acetate:chloroform:ethyldimethylamine eluent) to provide iodoenamide **222** (398.5 mg, 85% yield): R_F 0.38 (10:10:80 ethyl acetate:methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 5.41 (s, 1H), 4.58 (d, *J* = 1.8 Hz, 1H), 4.35-4.26 (comp m, 2H), 4.01-3.92 (comp m, 3H), 2.43 (s, 3H); ^{13}C

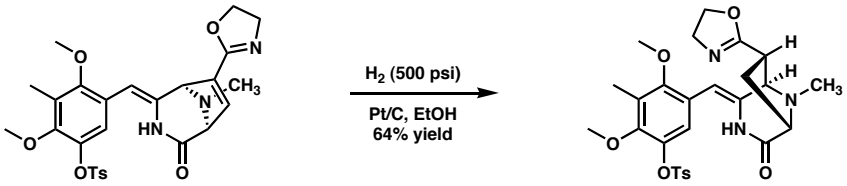
NMR (75 MHz, $CDCl_3$) δ 165.8, 159.6, 138.5, 135.7, 135.1, 71.6, 68.8, 67.6, 56.4, 55.3, 36.9; IR (NaCl/film) 3085, 2971, 2946, 1693, 1658, 1385, 1278, 1052 cm^{-1}; HRMS (FAB+) calc'd for $[C_{11}H_{12}N_3O_2I+H]^+$: *m/z* 346.0053, found 346.0041.



Styrene 221

To a solution of stannane **213** (70.8 mg, 115.8 μmol) and iodoenamide **222** (20 mg, 57.9 μmol) in dimethylsulfoxide (1.2 mL) were added copper(I) iodide (11.0 mg, 57.9 μmol) and tetrakis(triphenylphosphine)palladium(0) (6.7 mg, 5.8 μmol). The reaction mixture was deoxygenated by three times freezing under vacuum and thawing under argon, then sealed under argon and heated to 45 °C. After 24 h, the mixture was cooled to 22 °C, diluted with water (150 mL) and saturated aqueous ammonium hydroxide (10 mL), and extracted into ethyl acetate (50 mL, 35 mL). The organics were washed with half-saturated aqueous sodium chloride (50 mL) followed by saturated aqueous sodium chloride (25 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (1:99:1 to 5:95:1 ethanol:ethyl acetate: ethyldimethylamine eluent) to provide styrene **221** (24.8 mg, 79% yield): R_F 0.26 (10:90 ethanol:ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.82 (s, 1H), 5.57 (s, 1H), 4.45 (d, *J* = 1.5 Hz, 1H), 4.30 (app t, *J* = 9.6 Hz, 2H), 4.01-3.92 (comp m, 3H), 3.66 (s, 3H), 3.56

(s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.0, 154.1, 151.0, 145.5, 139.1, 136.0, 135.3, 133.4, 131.6, 129.9, 128.5, 127.5, 123.4, 122.4, 102.9, 71.8, 69.3, 67.5, 61.1, 60.2, 55.4, 37.3, 21.9, 9.9; IR (NaCl/film) 2941, 1692, 1659, 1372, 1191, 1177, 991, 551 cm^{-1}; HRMS (FAB+) calc'd for $[C_{27}H_{29}N_3O_7S+H]^+$: *m/z* 540.1804, found 540.1795.

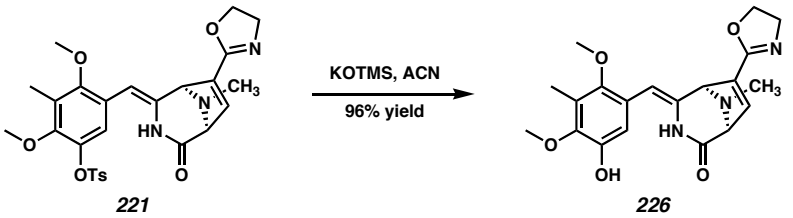


221 ***225***

Oxazoline 255

(Note: the reaction was performed in a stainless steel reaction vessel.) To a solution of styrene **221** (50 mg, 92.6 μmol) in anhydrous ethanol (1.8 mL) was added platinum on carbon (5% w/w, 15 mg). The reaction vessel was pressurized to 500 psi with hydrogen. After 11 h, the mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (90:5:5 to 80:10:10 ethyl acetate:acetonitrile:methanol eluent) to provide oxazoline **255** (32.0 mg, 64% yield): R_F 0.37 (10:10:80 methanol:ethyl acetate:chloroform); ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 5.42 (s, 1H), 4.23 (app td, *J* = 18.0, 9.0 Hz, 2H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.79-3.65 (comp m, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.53-3.46 (m, 1H), 2.64-2.52 (m, 1H), 2.51 (s, 3H), 2.49-2.40 (m, 1H), 2.46 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ

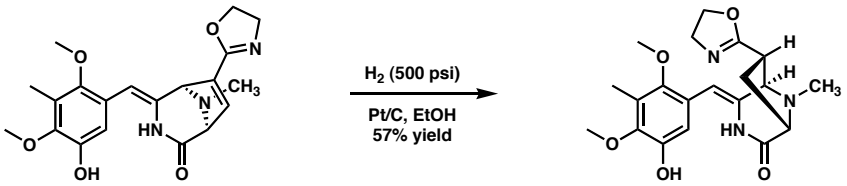
172.5, 169.3, 156.1, 152.1, 147.4, 140.4, 134.6, 134.3, 131.2, 129.6, 128.6, 125.1, 123.0, 104.6, 69.4, 68.0, 66.6, 61.5, 54.8, 43.1, 36.0, 32.7, 21.8, 9.8; IR (NaCl/film) 2944, 1691, 1482, 1372, 1191, 1176, 990 cm^{-1}; HRMS (FAB+) calc'd for $[C_{27}H_{31}N_3O_7S+H]^+$: *m/z* 542.1961, found 542.1971.



Phenol 226

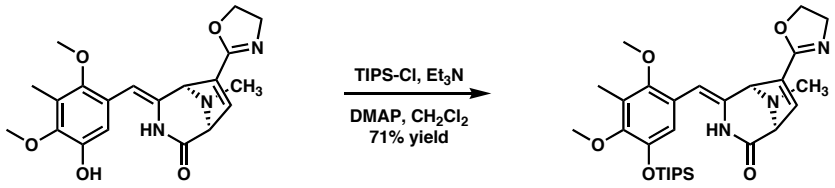
To a solution of tosylate **221** (758 mg, 1.40 mmol) in acetonitrile (14 mL) was added potassium trimethylsilanoate (90% grade, 998 mg, 7.0 mmol). After 1h 15 min, the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride (20 mL) for 10 min. The mixture was diluted with saturated aqueous sodium chloride (150 mL) and extracted into ethyl acetate (75 mL, 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (1:20:79:1 to 5:20:75:1 methanol:ethyl acetate:chloroform:ethyldimethylamine eluent) to provide phenol **226** (518 mg, 96% yield): R_F 0.37 (10:10:80 methanol:ethyl acetate:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.28 (br s, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.52 (s, 1H), 5.63 (s, 1H), 4.47 (s, 1H), 4.27 (app t, *J* = 9.5 Hz, 2H), 3.99-3.89 (comp m, 3H), 3.71 (s, 3H), 3.49 (s, 3H), 2.46 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 160.2, 148.4, 146.0, 145.9, 136.4, 134.9, 130.0, 125.6, 123.2, 114.4, 104.5, 70.5, 68.8, 67.5, 60.5, 60.3, 55.0, 37.0, 9.7; IR (NaCl/film) 3251 br, 2938,

1389, 1656, 1234, 1051, 1003, 731 cm^{-1}; HRMS (FAB+) calc'd for $[C_{20}H_{23}N_3O_5+H]^+$: *m/z* 386.1716, found 386.1735.



Oxazoline 220

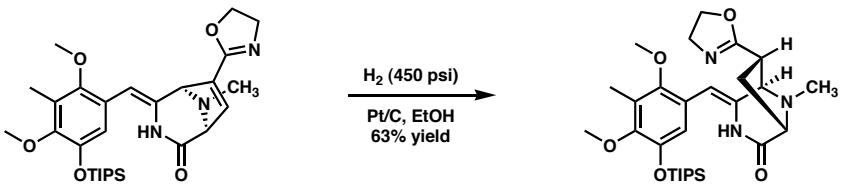
(Note: the reaction was performed in a stainless steel reaction vessel.) To alkene **226** (59.3 mg, 153.8 μmol) in anhydrous ethanol (2 mL) was added platinum on carbon (5% w/w, 23 mg). The reaction vessel was pressurized with hydrogen to 500 psi. After 3 h, the reaction mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (80:10:10 to 70:15:15 ethyl acetate:acetonitrile:methanol eluent) to provide oxazoline **220** (34.0 mg, 57% yield): R_F 0.26 (70:15:15 ethyl acetate:acetonitrile:methanol); ^{1}H NMR (300 MHz, CD_3OD) δ 6.53 (s, 1H), 5.41 (s, 1H), 4.23-4.15 (comp m, 2H), 4.00 (d, *J* = 6.3 Hz, 1H), 3.81-3.62 (comp m, 2H), 3.76 (s, 3H), 3.61 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 3.52-3.44 (m, 1H), 2.63-2.52 (m, 1H), 2.51 (s, 3H), 2.48 (app td, *J* = 13.5, 5.7 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.5, 169.4, 149.6, 148.0, 147.5, 132.6, 127.0, 124.4, 115.2, 106.3, 69.4, 68.1, 66.5, 61.1, 60.7, 54.8, 43.1, 36.0, 32.8, 9.9; IR (NaCl/film) 3251 br, 2943, 1666, 1483, 1453, 1325, 1236, 1006 cm^{-1}; HRMS (FAB+) calc'd for $[C_{20}H_{25}N_3O_5+H]^+$: *m/z* 388.1872, found 388.1870.



226 *227*

Silyl Ether 227

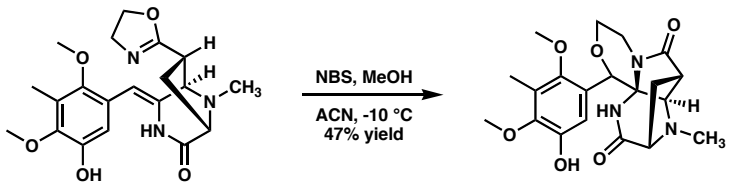
To a solution of phenol **226** (100 mg, 259.4 μmol) in dichloromethane (2.6 mL) were added triethylamine (181 μL, 1.30 mmol), 4-dimethylaminopyridine (7.9 mg, 64.8 μmol), and triisopropylsilyl chloride (167 μL, 778.2 μmol), in that order. After 52 h, the reaction mixture was diluted with water (50 mL) and extracted into dichloromethane (25 mL, 15 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:90:10:1 to 1:99:0:1 methanol:ethyl acetate:hexanes:ethyldimethylamine eluent) to provide silyl ether **227** (99.0 mg, 71% yield): R_F 0.61 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.49 (s, 1H), 5.58 (s, 1H), 4.47 (s, 1H), 4.30 (app t, *J* = 9.9 Hz, 2H), 4.02-3.91 (comp m, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 2.52 (s, 3H), 2.17 (s, 3H), 1.32-1.19 (comp m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.2, 149.3, 148.9, 145.9, 136.1, 135.1, 130.2, 126.6, 122.7, 118.7, 104.5, 71.8, 69.3, 67.5, 60.3, 60.2, 55.3, 37.3, 18.1, 13.0, 9.8; IR (NaCl/film) 2944, 2867, 1694, 1659, 1482, 1242, 1064, 882 cm^{-1}; HRMS (FAB+) calc'd for $[C_{29}H_{43}N_3O_5Si+H]^+$: *m/z* 542.3050, found 542.3053.



227 *228*

Oxazoline 228

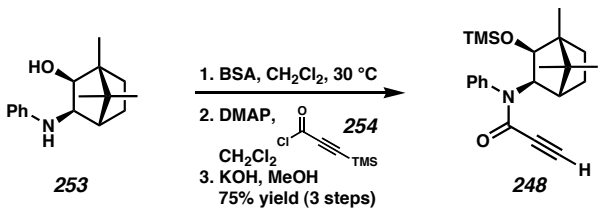
(Note: the reaction was performed in a stainless steel reaction vessel.) To alkene **227** (94.0 mg, 173.6 μmol) in anhydrous ethanol (1.7 mL) was added platinum on carbon (5% w/w, 27 mg, 6.9 μmol). The reaction vessel was pressurized with hydrogen to 450 psi. After 2 h, the reaction mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (1:99:0.5 to 5:95:0.5 methanol:ethyl acetate:ethyldimethylamine eluent) to provide oxazoline **228** (59.0 mg, 63% yield): R_F 0.34 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD) δ 6.57 (s, 1H), 5.42 (s, 1H), 4.29-4.15 (comp m, 2H), 4.04 (d, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76-3.64 (comp m, 2H), 3.36 (s, 3H), 3.53 (d, *J* = 7.5 Hz, 1H), 3.52-3.46 (m, 1H), 2.65-2.53 (m, 1H), 2.52 (s, 3H), 2.46 (app td, *J* = 13.7, 5.6 Hz, 1H), 2.21 (s, 3H), 1.35-1.21 (comp m, 3H), 1.13 (d, *J* = 6.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.7, 149.3, 149.2, 146.0, 132.1, 126.9, 123.0, 118.1, 104.0, 67.9, 66.9, 65.1, 60.3, 60.2, 54.5, 42.3, 35.7, 32.3, 18.1, 13.0, 9.8; IR (NaCl/film) 2944, 2867, 1696, 1666, 1482, 1241, 1064, 1012, 882 cm^{-1}; HRMS (FAB+) calc'd for $[C_{29}H_{45}N_3O_5Si+H]^+$: *m/z* 544.3207, found 544.3219.



220 *237*

Pyrrolidinone 237

To a –10 °C solution of oxazoline **220** (35.0 mg, 90.3 μmol) and methanol (36.5 μL, 903 μmol) in acetonitrile (903 μL) was added *N*-bromosuccinimide (17.7 mg, 99.3 μmol). After 15 min, the reaction mixture was partially purified by flash chromatography on silica gel (0:0:100 to 15:15:70 methanol:acetonitrile:ethyl acetate eluent). The resulting mixture of products was further purified by flash chromatography on silica gel (0:100:1 to 10:90: methanol:ethyl acetate eluent:ethyldimethylamine eluent) to provide pyrrolidinone **237** (17.0 mg, 47% yield): R_F 0.37 (15:15:70 methanol:acetonitrile:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.94 (s, 1H), 6.51 (s, 1H), 5.43 (s, 1H), 3.86 (d, *J* = 5.7 Hz, 1H), 3.84 (s, 3H), 3.84-3.77 (comp m, 2H), 3.66 (app td, *J* = 12.0, 5.4 Hz, 1H), 3.52 (d, *J* = 7.2 Hz, 1H), 3.32 (app td, *J* = 13.8, 4.5 Hz, 1H), 3.05-2.97 (m, 1H), 2.57-2.43 (m, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 1.94 (dd, *J* = 13.7, 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 172.0, 152.3, 147.1, 145.0, 126.5, 122.3, 113.6, 73.6, 72.9, 65.1, 64.8, 62.5, 60.8, 56.9, 42.9, 37.1, 36.2, 31.0, 10.2; IR (NaCl/film) 3245 br, 2943, 1673, 1453, 1417, 1113, 1008 cm^{-1}; HRMS (EI+) calc'd for $[C_{20}H_{25}N_3O_6]^{\bullet+}$: *m*/*z* 403.1743, found 403.1743.



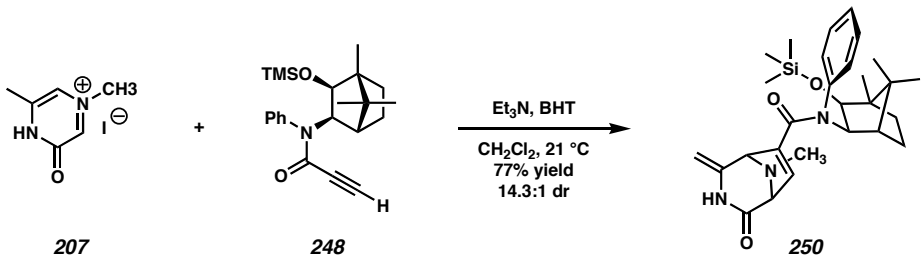
Alkynamide 248

To a 30 °C solution of amino alcohol **253** (1.008 g, 4.10 mmol) in dichloromethane (10.2 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (4.05 mL, 16.4 mmol). After 15 h, additional *N*,*O*-bis(trimethylsilyl)acetamide (1.01 mL, 4.09 mmol) was added. After an additional 6 h, the reaction mixture was concentrated and purified by flash chromatography on silica gel (4:96 ethyl acetate:hexanes eluent) to provide the silyl ether (1.18 g, 91% yield).

To a solution of trimethylsilyl propynoic acid (247.3 mg, 1.74 mmol) and dimethylformamide (16 μL, 207 μmol) in dichloromethane (1.6 mL) was added oxalyl chloride (156 μL, 1.79 mmol) (caution: gas evolution). After 20 min, a solution of 4-dimethylaminopyridine (147.4 mg, 1.21 mmol) and the step-one silyl ether (152.3 mg, 480 μmol) in dichloromethane (1.6 mL) was added dropwise over 1 min. After an additional 15 min, the reaction mixture was diluted with dichloromethane (25 mL) and washed with saturated aqueous ammonium chloride (2 x 25 mL) followed by saturated aqueous sodium chloride (15 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (4:96 ethyl acetate:hexanes eluent) to provide the *C*-trimethylsilyl alkynamide.

To a solution of *C*-trimethylsilyl alkynamide (2.01 g, 4.6 mmol) in methanol (60 mL) was added anhydrous potassium hydroxide (660 mg, 11.8 mmol). After 5 min, the

reaction mixture was diluted in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 ethyl acetate:hexanes eluent) to provide alkynamide **248** (1.54 g, 91% yield) as a pale yellow oil: R_F 0.32 (15:85 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCL_3$) δ 7.45-7.30 (comp m, 4H), 7.14-7.02 (m, 1H) 4.30 (d, *J* = 6.6 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 1H), 2.72 (s, 1H), 1.94 (d, *J* = 2.1 Hz, 1H), 1.78-1.62 (m, 1H), 1.51-1.36 (m, 1H), 1.28-1.12 (comp m, 2H), 0.82 (s, 3H), 0.58 (s, 3H), 0.50 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 140.6, 133.7, 130.6, 128.4, 128.3, 83.4, 79.5, 66.9, 49.5, 47.3, 47.0, 32.4, 29.0, 21.9, 21.7, 12.9, 0.9; IR (NaCl/thin film) 2960, 2106, 1634, 1594, 1491, 1344, 839 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{22}H_{32}NO_2Si+H]^+$: 370.2202, found 370.2193.



207 *248* *250*

Diazabicycle 250

To a 21 °C suspension of pyrazinone **207** (114.1 mg, 453 μmol) in dichloromethane (2.5 mL) were added alkynamide **248** (500.7 mg, 1.35 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (20.0 mg, 91 μmol). Et_3N (66.0 μL, 474 μmol) was then added in four portions at 2 h intervals. The solution was maintained at 21 °C for an additional 22 h, then diluted with dichloromethane (50 mL) and washed with saturated

aqueous ammonium chloride (2 x 50 mL) followed by brine (50 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 75:25 ethyl acetate:hexanes eluent) to yield diazabicycle **250** (173.1 mg, 77% yield, 14.3:1 dr) as a white solid: R_F 0.27 (75:25 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 4H), 7.14-7.02 (m, 1H), 5.55 (d, *J* = 2.7 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 1H), 4.32 (s, 1H), 4.19 (d, *J* = 1.2 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 1H), 3.62-3.60 (m, 1H), 2.08 (s, 3H), 1.78-1.62 (m, 1H), 1.50-1.34 (m, 1H), 1.28-1.10 (comp m, 2H), 0.80 (s, 3H), 0.58 (s, 3H), 0.47 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 164.0, 141.6, 141.2, 137.9, 135.6, 128.8, 128.6, 93.2, 83.9, 71.9, 69.8, 68.2, 49.5, 47.2, 47.1, 37.3, 32.5, 29.5, 22.2, 21.7, 13.0, 1.0; IR (NaCl/thin film) 3224, 2954, 1691, 1634, 1591, 1495, 1349, 903, 839 cm^{-1}; LRMS (APCI) *m/z* calc'd for $[C_{28}H_{39}N_3O_3Si+H]^+$: 494.3, found 494.2.

3.6 Notes and Citations

(1) For the isolation and crystallographic characterization of cyanocycline A, see: (a) Hayashi, T.; Noto, T.; Nawata, Y.; Okazaki, H.; Sawada, M.; Ando, K. *J. Antibiot.* **1982**, *35*, 771-777. (b) Hayashi, T.; Nawata, Y. *J. Chem. Soc. Perkin Trans. II* **1983**, 335-343.

(2) For a comprehensive review of the chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics, including cyanocycline A, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

(3) For the isolation of lemonomycin, see: (a) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83-86. For the structural determination of lemonomycin, see: (b) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067-2071.

(4) Our synthesis of (–)-lemonomycin is discussed in Chapter 2 of this thesis. See also: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000-15001.

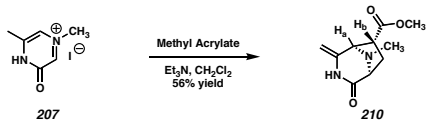
(5) A similar enamide has been advanced stereoselectively to a similar alcohol by epoxidation with dimethyldioxirane followed by reduction with sodium cyanoborohydride, see: Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095-3097.

(6) The diastereoselective hydrogenation of enamide **142** (Scheme 2.11, Chapter 2) provides empirical support for the ability of the diazabicyclic framework to direct reduction to the convex face of **204**.

(7) Lutz, W. B.; Lazarus, S.; Klutchko, S.; Meltzer, R. I. *J. Org. Chem.* **1964**, *29*, 415-418.

(8) This effect was first reported for diazabicyclooctane ring systems by Joule, see: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187-2190.

(9) Diazabicycle **210** was produced by the dipolar cycloaddition of **207** with methyl acrylate. H_a of **210** appears as a sharp singlet at $\delta = 3.99$ in $CDCl_3$.



(10) Semiempirical calculations at the AM1 level indicate that "endo" isomer **209** is 3.1 kcal/mol less stable than "exo" isomer **210**. These calculations were performed with Spartan '02 v1.0.8 (Wavefunction, Inc.).

(11) For reviews of transition metal-catalyzed coupling reactions, see: (a) Diederich, F.; Stang, P. J.; Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.10, pp 158.

(c) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Wiley: Chichester, 2000; Chapter 3, pp 27.

(12) For examples of copper(I) accelerated Stille reactions, see: (a) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029-12046. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600-7605. (c) For a review of the Stille reaction including copper(I) accelerated conditions, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652.

(13) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges*. **1911**, *44*, 2030-2036. For a recent review of the Pictet-Spengler cyclization, see: (b) Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797-1842.

(14) This oxazoline synthesis is based on the Bristol-Meyers-Squibb modification of Nishiyama's oxazoline synthesis, see: (a) Totleben, M. J.; Prasad, J. S.; Simpson, J. H.; Chan, S. H.; Vanyo, D. J.; Kuehner, D. E.; Deshpande, R.; Kodersha, G. A. *J. Org. Chem.* **2001**, *66*, 1057-1060. (b) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306-4309.

(15) (a) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781-4782. (b) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331-347. Also, see reference 8.

(16) (a) Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745-3748.

(b) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919-3920.

(17) The analogous Suzuki coupling of **222** with aryl boronate **156** provided at best 54% yield of styrene **221**.

(18) These conditions utilized $Pd(PPh_3)_4$ (10 mol%), LiCl (6 equiv), and CuCl (5 equiv) in DMSO at 70 °C, see reference 12b.

(19) This Stille coupling provided good conversion to the styrene on preparative scale. However, difficulties in separating the highly polar product from dimethylsulfoxide resulted in somewhat lower yields (65% yield or better).

(20) The stereochemistry of hydrogenation products **225**, **220**, and **228** was assigned by the appearance of doublets for both bridgehead protons in the ^1H NMR. See the discussion of this effect for **209** (Scheme 3.3).

(21) A second product, apparently diastereomeric to **237**, was isolated from the oxidation of **220** with NBS. Such a diastereomer could easily result from quinone-methide cation **236**, but is less likely to result from S_N2 displacement of bromide **235**. We therefore favor the mechanism involving **236**.

(22) The HETCOR was taken in $CDCl_3$ with decoupling at 300 MHz and observation at 75 MHz.

(23) A similar sequence was utilized in the Evans synthesis of cyanocycline A, see: (a) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1907-1910. (b) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1911-1914. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478-2479. (d) Biller, S. A. An Approach to the Total Synthesis of (±)-Naphthyridinomycin A. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1982.

(24) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239-4254.

(25) Shi, M.; Wang, C.-J. *J. Chem. Res*. **2004**, *2*, 107-110.

(26) The diastereomeric ratios of **243** and **245** were determined by ^{1}H NMR integrations of the crude reaction mixtures. These compounds were not further purified or characterized.

(27) In this case, orientation of the three-carbon dipole unit over the auxiliary's carbonyl oxygen is termed "endo," while approach of the three-carbon unit over the ester oxygen (or amide nitrogen) is termed "exo."

(28) This work was performed in collaboration with Kevin Allan, a graduate student in the Stoltz research group.

(29) The conformation of **248** was minimized with semiempirical calculations at the AM1 level. These calculations were performed with Spartan '02 v1.0.8 (Wavefunction, Inc.).

(30) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett*. **1983**, *24*, 3213-3216.