CHAPTER TWO

The First Total Synthesis of (–)-Lemonomycin

2.1 Synthetic Planning for (–)-Lemonomycin

Structure and Synthetic Challenges

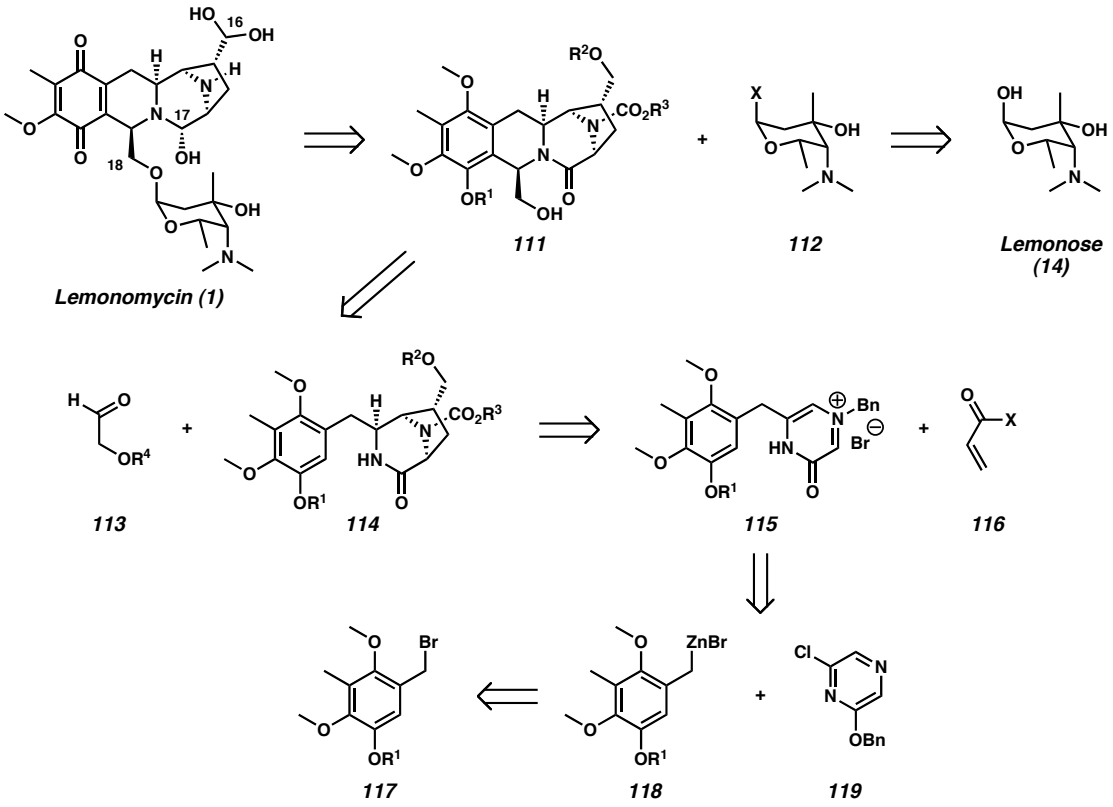
Lemonomycin (**1**, Scheme 2.1) presents an array of challenges to the synthetic chemist.[1] The natural product incorporates a stereochemically dense tetracyclic core bound through the C(18) oxygen to a complex 2,6-dideoxy-4-aminopyranose. The compound contains a total of ten stereocenters, including two sets of three contiguous stereogenic carbons. Lemonomycin also displays a variety of chemically sensitive groups, including one secondary and two tertiary amines, as well as quinone, carbinolamine, aldehyde hydrate, acetal, and tertiary alcohol functionality. Additionally, no reports concerning synthetic routes toward lemonomycin had appeared in the literature prior to our work,[2] so the potential pitfalls of any synthetic plan were unknown.

Original Retrosynthesis

In our analysis of lemonomycin, we envisioned the natural product arising from alcohol **111** by late stage glycosylation with a lemonose synthon such as **112** followed by adjustment of the oxidation states of the arene, C(16), and C(17) (Scheme 2.1). Alcohol **111** would in turn be derived from amide **114** and aldehyde **113** by a Pictet-Spengler cyclization.[3,4] We then recognized the diazabicyclooctane moiety as a retron for a dipolar cycloaddition transform, revealing dipole precursor **115** and acrylate **116**. Potentially, asymmetry could be introduced in this step through the use of either a chiral Lewis acid

catalyst or a chiral auxiliary on the acrylate fragment. Dipole precursor **115** was simplified by a Negishi coupling transform to unveil benzylic zinc bromide **118** and chloropyrazine **119**. The organozinc reagent was expected to be readily accessible from benzylic bromide **117**.

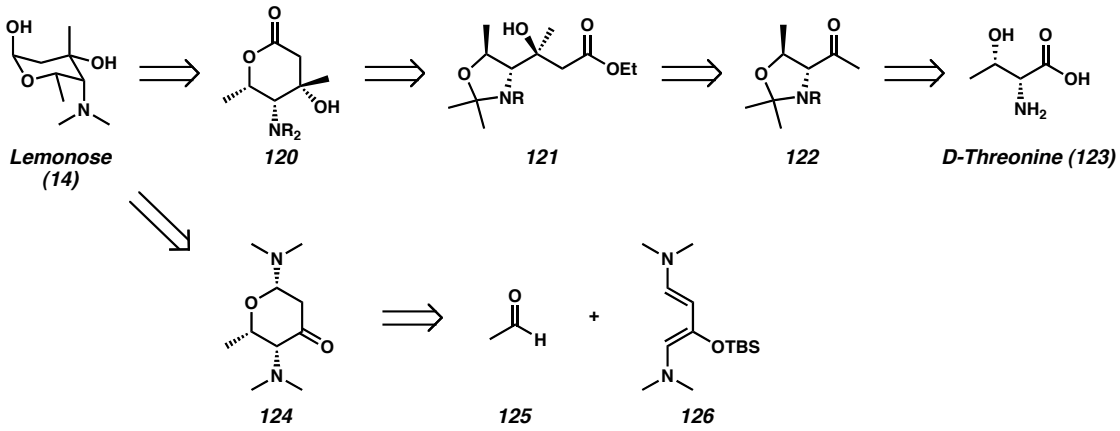
Scheme 2.1 Retrosynthetic Analysis of Lemonomycin



We anticipated that a glycosyl precursor (**112**) could be readily synthesized from lemonose (**14**). Lemonose could be generated by diastereoselective reduction of lactone **120**, which could in turn arise by hydrolysis and cyclization from ester **121** (Scheme 2.2). Application of a Felkin-Ahn-controlled diastereoselective aldol transform to ester **121** revealed methyl ketone **122**, which was expected to be available from D-threonine (**123**).[5]

A second possible strategy for the synthesis of lemonose (**14**) involves hetero-Diels-Alder chemistry. Lemonose could be derived by methyl anion addition and hydrolysis from aminopyranone **124**. This pyranone could be simplified by the application of a catalytic asymmetric hetero-Diels-Alder transform to reveal diene **126** and acetaldehyde (**125**) as starting materials.[6]

Scheme 2.2 Retrosynthetic Analysis of Lemonose



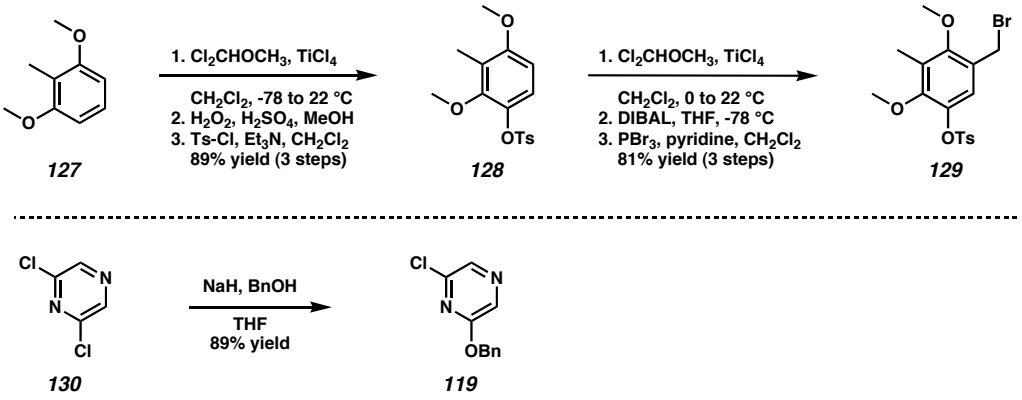
2.2 Early Synthetic Work

Dipole Synthesis

Our first targets thus became the reagents for the Negishi coupling reaction, specifically benzylic bromide **129** and chloropyrazine **119** (Scheme 2.3). The synthesis of **129** began with 2,6-dimethoxytoluene (**127**), which was converted to tosylate **128** by a formylation, Baeyer-Villiger oxidation under hydrolytic conditions, and reaction with tosyl chloride.[7] Recrystallization of **128** proved to be the only necessary purification in this sequence. Tosylate **128** was then converted to benzylic bromide **129** by a three-step procedure of formylation, DIBAL reduction to the alcohol, and treatment with

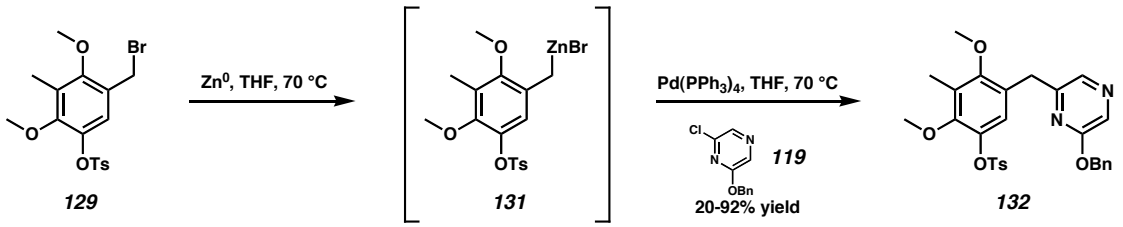
phosphorus tribromide and pyridine. The only necessary purification along this route was a rapid silica gel filtration of the final reaction mixture. Chloropyrazine **119** was readily synthesized from commercially available 2,6-dichloropyrazine (**130**) by selective mono substitution with in situ generated sodium benzyloxide.[8]

Scheme 2.3 Synthesis of the Negishi Coupling Partners



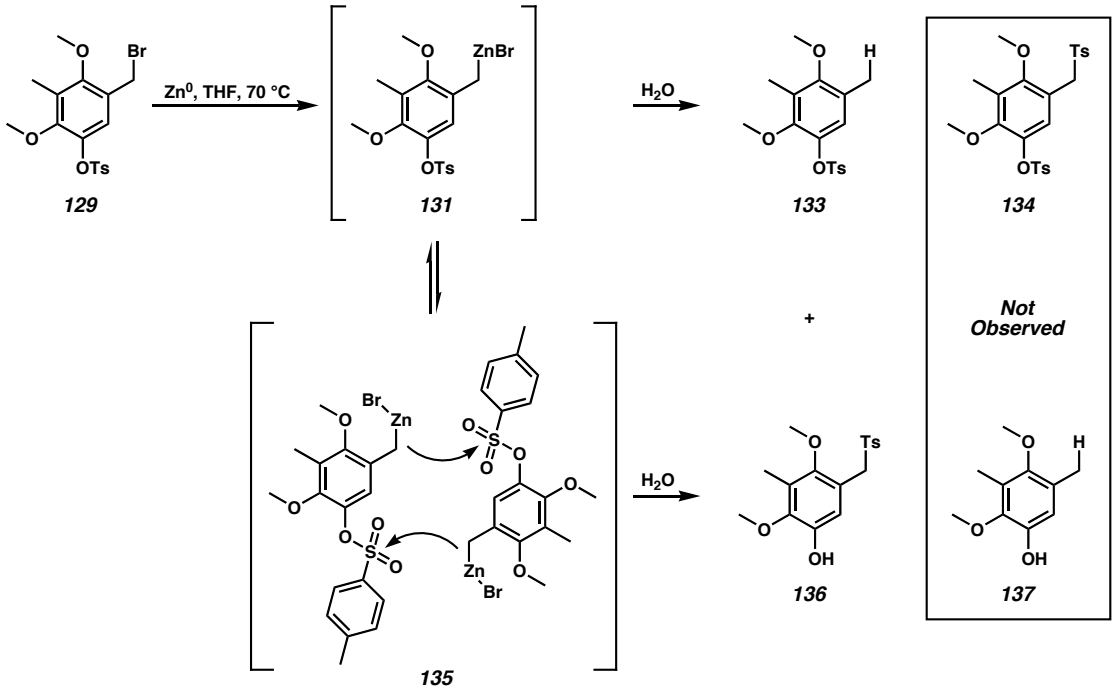
With the coupling partners in hand, we turned our attention to the Negishi reaction (Scheme 2.4). It was quickly discovered that reaction of bromide **129** with zinc dust[9] in tetrahydrofuran followed by addition of chloropyrazine **119** and a palladium(0) catalyst effected facile coupling to bisarene **132**.[10] The results of this reaction, unfortunately, were highly inconsistent, providing yields that varied between 20% and 92%. After extensive investigation, it was found that reproducibility could not be attained despite adjustments to the solvent, temperature, catalyst, or catalyst loading of the palladium-catalyzed step.

Scheme 2.4 Negishi Coupling Reaction



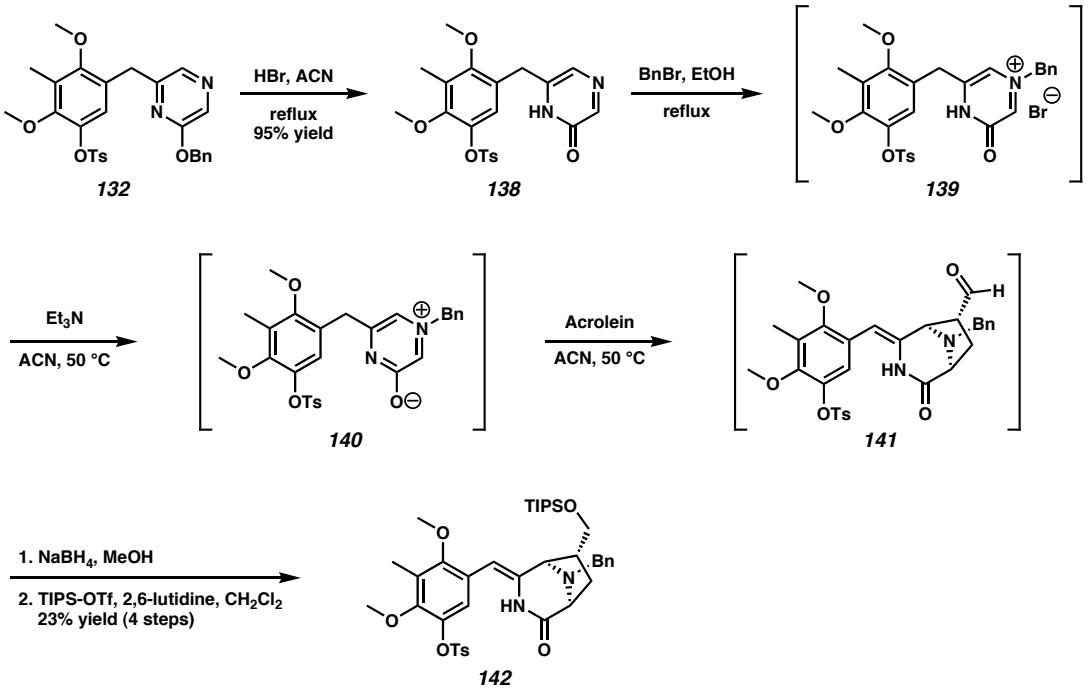
The zinc-insertion step of the Negishi sequence was therefore investigated by treating bromide **129** with zinc dust, heating the solution to 70 °C, and quenching the reaction with water (Scheme 2.5). This reaction provided the expected desbromo toluene **133**, which is generated by protonolysis of putative benzylic zinc intermediate **131**. To our surprise, however, a sulfonyl-transfer product (**136**) was also isolated in amounts that varied unpredictably over several reaction trials. Importantly, neither disulfonyl arene **134** nor the fully desulfonylated product (**137**) was isolated. We therefore propose that **136** must arise through a multimeric complex such as **135**, wherein the two sulfonyl-transfer events occur more rapidly than dissociation of the complex.[11,12] The association of organometallic **131** into a complex such as **135** could occur through π-stacking forces, coordination of the sulfonyl oxygen atoms to cationic zinc centers, or bridging Zn-Br-Zn interactions. Unfortunately, attempts to control the extent of sulfonyl transfer by the use of alternative solvent, the introduction of aromatic cosolvent to impede π-stacking, the presence or absence of oxygen, and the use of different batches of starting material and reagents failed to induce or prevent sulfonyl transfer in any consistent way. We were therefore unable to improve the reliability of the Negishi coupling sequence.

Scheme 2.5 Unexpected Sulfonyl Transfer Reaction



Despite the inconsistency of the Negishi coupling reaction, gram quantities of bisarene **132** could be produced. This compound was advanced by acidic benzyl ether cleavage to pyrazinone **138** (Scheme 2.6). Alkylation of the pyrazinone with benzyl bromide provided oxidopyrazinium **139** as an unstable oil. Treatment of this salt with triethylamine and acrolein generated an inseparable mixture of cycloadducts **141** through the intermediacy of dipole **140**.[13,14,15] After reduction and silylation, diazabicyclooctane **142** could be isolated as a single isomer. Unfortunately, due to the instability of **139** and **140** and the formation of isomers in the cycloaddition reaction, the yield of **142** could not be improved beyond 23% over the four steps.

Scheme 2.6 Dipolar Cycloaddition

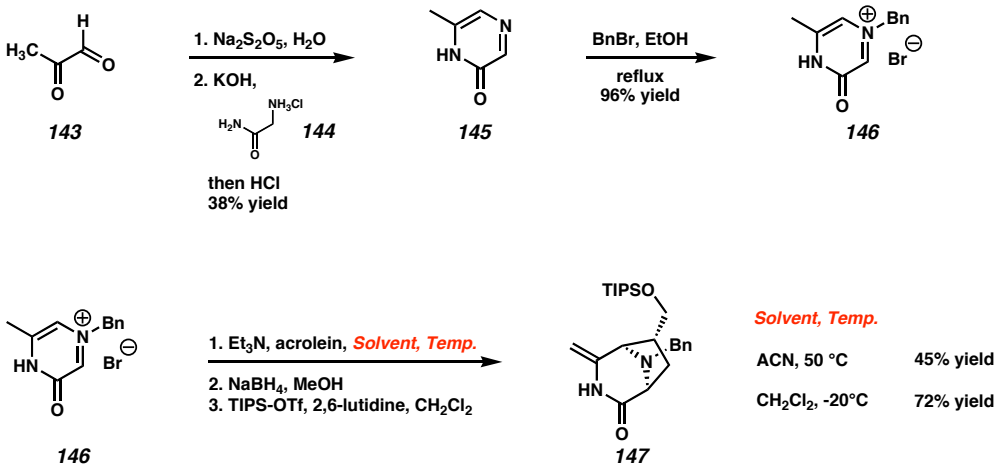


Optimization of the Dipolar Cycloaddition

In light of the difficulty in synthesizing pyrazinone **138** and the unstable nature of oxidopyrazinium salt **139**, we decided to optimize the dipolar cycloaddition with the simple oxidopyrazinium salt **146**.[16] Oxidopyrazinium **146** was readily synthesized by known procedures. Thus, cyclocondensation of glycinamide hydrochloride (**144**) with pyruvaldehyde (**143**) followed by alkylation of the resulting pyrazinone **145** with benzyl bromide provided **146** as a bench-stable powder (Scheme 2.7).[17] When this compound was treated with triethylamine and acrolein in acetonitrile at 50 °C, a mixture of inseparable cycloadducts again resulted, with a single isomer (**147**) available in 45% yield after reduction and silylation. Gratifyingly, the yield of silyl ether **147** could be

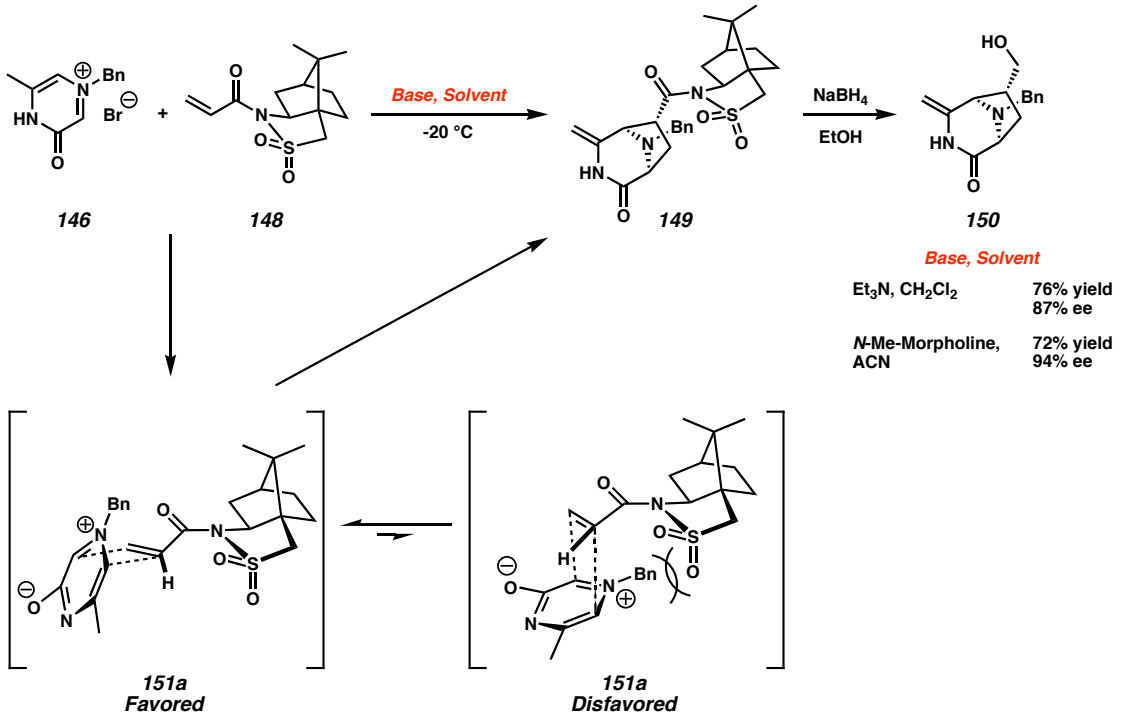
increased to 72% by performing the cycloaddition reaction in dichloromethane at –20 °C. The increased yield was primarily due to the minimization of other cycloadduct isomers.

Scheme 2.7 Cycloaddition Optimization with a Simple Dipole



Having developed optimized conditions for the dipolar cycloaddition of **146** with acrolein, we investigated the use of chiral auxiliaries for the production of enantioenriched diazabicyclic compounds. The acrylamide of Oppolzer's sultam (**148**)[18] was tested due to its well-precedented use in dipolar cycloadditions of nitrile oxides, silyl nitronates, and azomethine ylides.[19,20] To our delight, under the conditions utilized for our racemic cycloaddition, this acrylamide provided good diastereocontrol in the production of **149**, such that alcohol **150** could be isolated in 87% ee after reductive cleavage of the auxiliary (Scheme 2.8). After a screen of conditions, it was found that **150** could be produced with 94% ee if *N*-methyl morpholine was utilized as the base and acetonitrile as the solvent.[21]

Scheme 2.8 Asymmetric Dipolar Cycloaddition



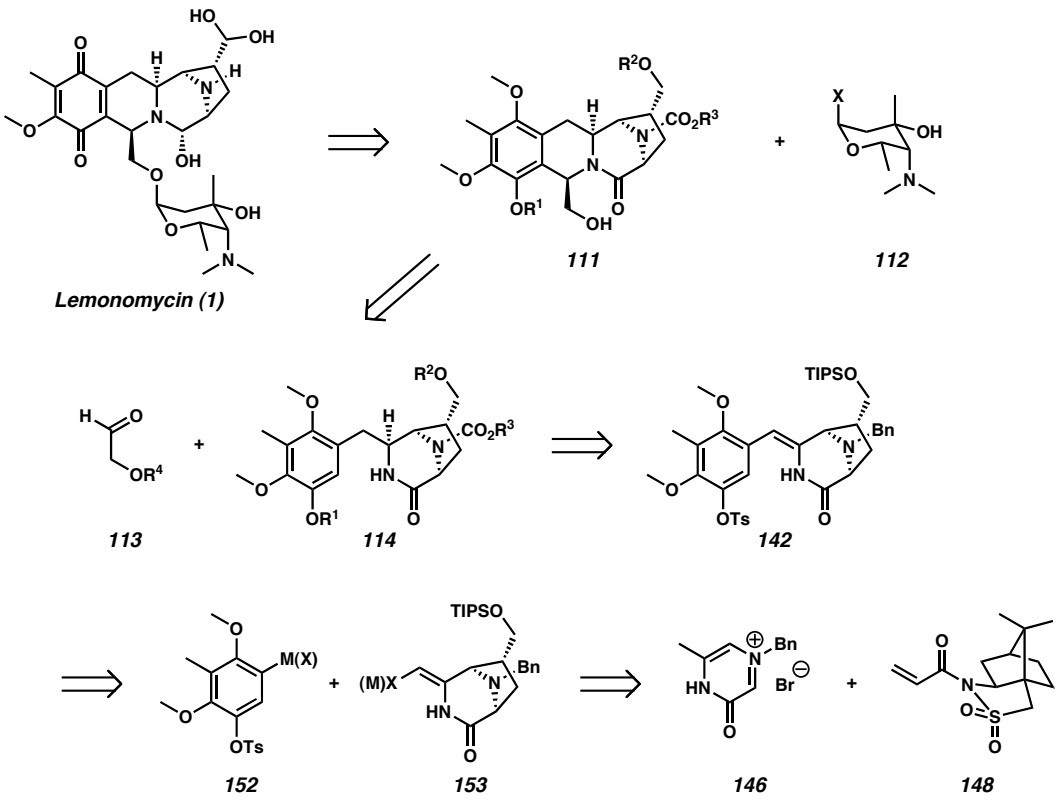
In analogy to proposed models,[19] the cycloaddition of **146** with **148** is expected to occur through transition state **151**. The conformation of the acrylamide is controlled by lone pair repulsion and by the steric influence of the amide. Lone pair repulsion causes the carbonyl oxygen to rotate away from the sulfonamide oxygen atoms, placing the C-O double bond and the N-S bond in an *s-trans* orientation. The steric influence of the amide forces the acrylamide olefin and carbonyl into an *s-cis* geometry. In this conformation, the pseudoaxial sulfonamide oxygen blocks the lower face of the alkene. Cycloaddition across the top face of the alkene yields **149**.

2.3 Second Generation Approach to (–)-Lemonomycin

Revised Synthetic Plan

Our success in developing an asymmetric, high-yielding route to alcohol **150** encouraged us to utilize this compound as an intermediate in the synthesis of (–)-lemonomycin. We therefore revised our retrosynthetic plan to include the early-stage asymmetric dipolar cycloaddition (Scheme 2.9). It was still expected that the natural product could be derived from **114** by a Pictet-Spengler cyclization and late-stage glycosylation (*vide supra*). However, lactam **114** was now simplified by the application of a diastereoselective hydrogenation transform and protecting group manipulations to reveal styrene **142**, which contains a retron for a palladium catalyzed coupling reaction.[22] Application of this transform unveiled arene **152** with either a halide or metallic substituent and enamide **153** with the opposite functionality. The enamide was expected to be readily accessible from oxidopyrazinium **146** and acrylamide **148** through our dipolar cycloaddition protocol.

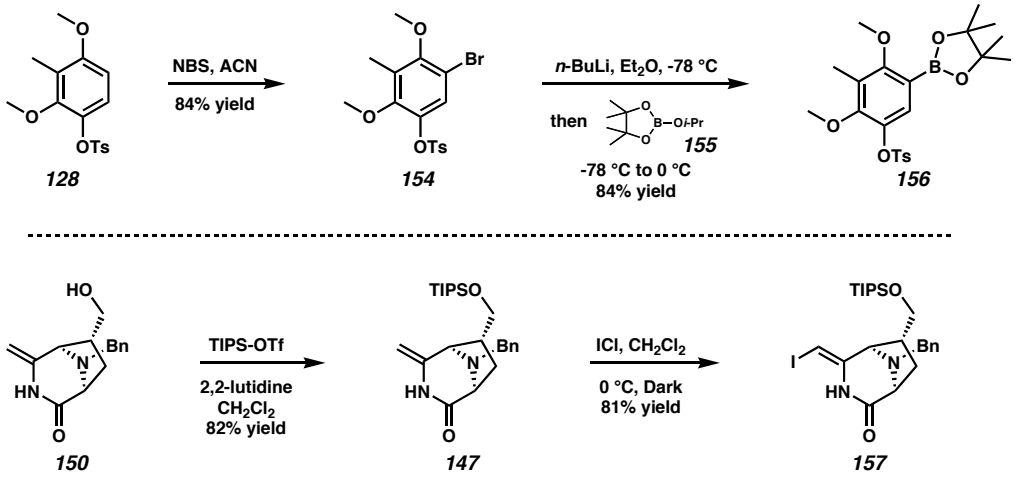
Scheme 2.9 Revised Retrosynthesis of (–)-Lemonomycin



Styrene Synthesis

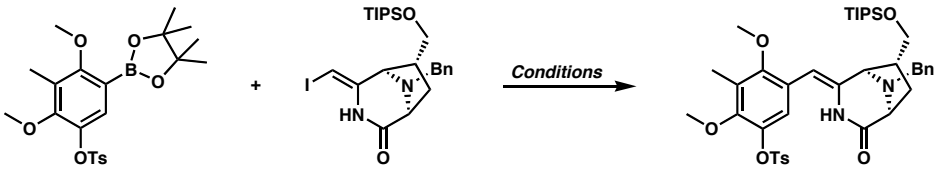
With a new synthetic plan in mind, we investigated the synthesis of styrene **142**. To this end, arene **128** was cleanly brominated to provide **154**, which could be converted to boronic ester **156** by lithium-bromide exchange and quenching with boronate **155** (Scheme 2.10). Alcohol **150** was converted to silyl ether **147** under standard conditions. Attempts to convert the enamide of **147** to an organometallic reagent by either hydroboration or mercuration were unsuccessful, but the enamide was readily iodinated with iodine monochloride to provide vinyl iodide **157**. Boronate **156** and iodide **157** were expected to be useful substrates for a Suzuki coupling reaction.[23]

Scheme 2.10 Synthesis of the Suzuki Substrates



With boronic ester **156** and vinyl iodide **157** in hand, we investigated the Suzuki coupling reaction (Table 1).[24] A variety of standard conditions gave poor results, but we were pleased to find that reaction with catalytic tetrakis(triphenylphosphine)palladium(0) and aqueous sodium carbonate provided a moderate yield of styrene **142** (Entry 5). The use of lithium carbonate as the stoichiometric base was less effective (Entry 4), but improved yields of coupled product were obtained when either potassium or cesium carbonate was employed as the base (Entries 6 and 7). Moreover, these reactions required only 5 mol% palladium for efficient catalysis. Importantly, the coupling reaction with potassium carbonate as base was effective on multigram scale, although a slight drop in yield was observed (Entry 8).

Table 2.1 Suzuki Coupling



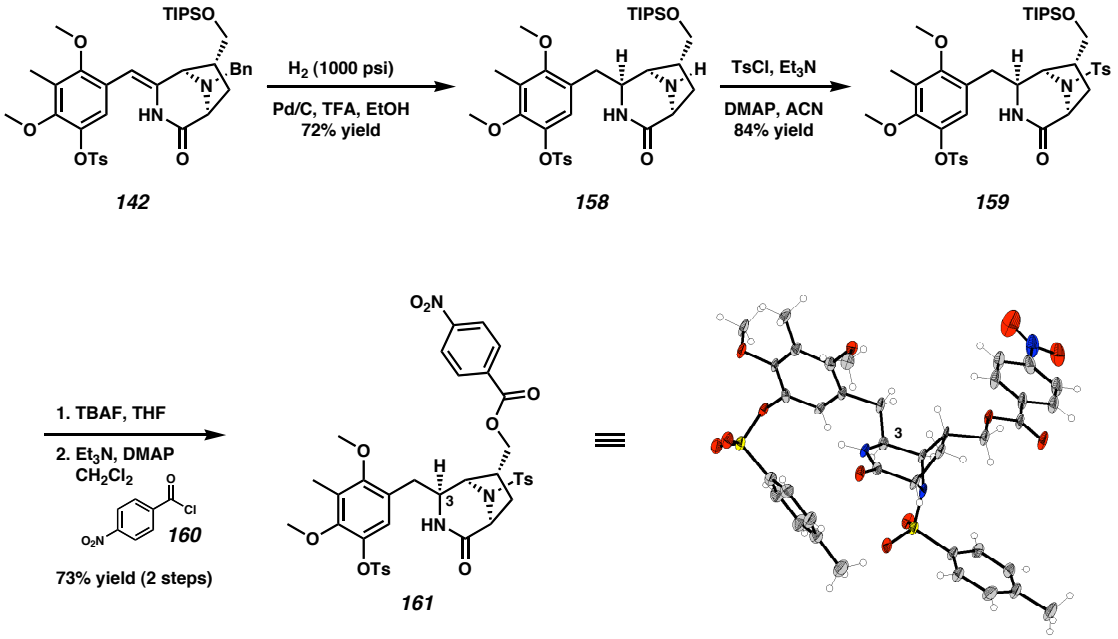
Entry	*Conditions*		*Yield*
1	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol%), KOAc, DMSO, 80 °C		0%
2	$PdCl_2(dppf)\cdot CH_2Cl_2$ (20 mol%), K_3PO_4, DME, 85 °C		trace
3	$Pd(PPh_3)_4$ (10 mol%), $Ba(OH)_2$, DME, H_2O, 75 °C		49%
4	$Pd(PPh_3)_4$ (10 mol%), Li_2CO_3 (aq), Benzene, MeOH, 70 °C		44%
5	$Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (aq), Benzene, MeOH, 70 °C		63%
6	*$Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (aq), Benzene, MeOH, 70 °C*		*73%*
7	$Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (aq), Benzene, MeOH, 70 °C		73%
8	*$Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (aq), Benzene, MeOH, 70 °C*	*3.1g Scale*	*69%*

Diastereoselective Reduction of the Enamide

The next challenge was hydrogenation of styrene **142** with necessary control of stereochemistry (Scheme 2.11). After substantial experimentation, it was discovered that carbon-supported palladium(0) in ethanol with an acidic cosolvent was uniquely effective for the reduction of **142**, although significant conversion (with concomitant benzyl amine hydrogenolysis) was observed only at high hydrogen pressures.[25] Use of trifluoroacetic acid as the acidic cosolvent provided lactam **158** as single diastereomer, while the use of acetic acid led to a mixture of **158** and an apparently diastereomeric compound.[26] To prove the stereochemistry of **158**, a crystalline substance was required.[27] Toward this end, treatment of amine **158** with tosyl chloride produced tosamide **159**. Silyl ether cleavage followed by acylation with 4-nitrobenzoyl chloride then provided ester **161** as a highly crystalline solid. X-ray diffraction analysis of a single crystal of **161** showed that

the stereochemistry at C(3)[28] matched the stereochemistry reported for the natural product.

Scheme 2.11 Diastereoselective Reduction of the Enamide

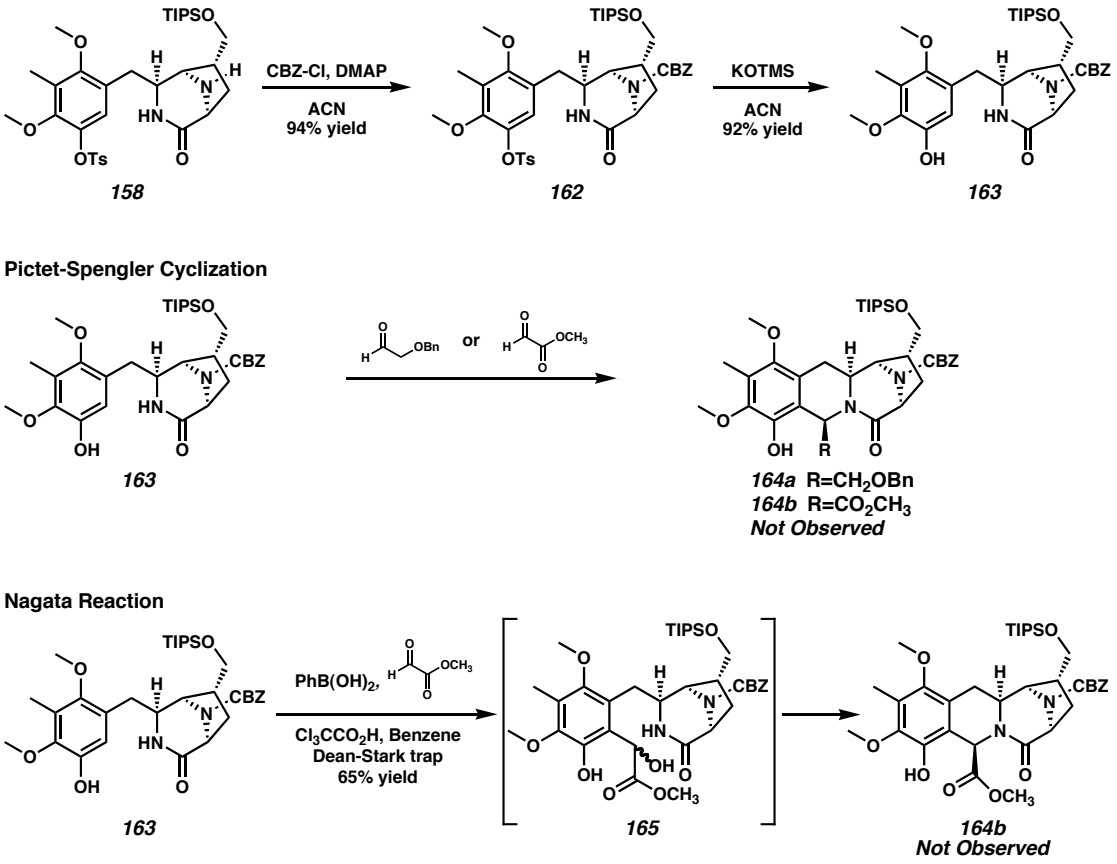


Pictet-Spengler Cyclization

Amide **158** was advanced synthetically by conversion of the amine to a urethane with CBZ-Cl and DMAP in acetonitrile (Scheme 2.12). Cleavage of the tosylate was effected with potassium trimethylsilanoate to provide phenol **163**, which was expected to be an effective substrate for Pictet-Spengler cyclization to tetrahydroisoquinoline **164**. Unfortunately, treatment of **163** with benzyloxyacetaldehyde under a variety of conditions failed to provide any cyclized product. In analogy to the protocol utilized by Evans for the synthesis of cyanocycline A,[29] we then attempted to condense **163** with

monomeric methyl glyoxylate. Unfortunately, these conditions also failed to cause any conversion of the starting material.

Scheme 2.12 Pictet-Spengler and Nagata Attempts



The proposed Pictet-Spengler cyclization would mechanistically form a carbon-nitrogen bond followed by a carbon-carbon bond. Due to the failure of the Pictet-Spengler protocols, we searched for a reaction that would allow for direct carbon-carbon bond formation. In this regard, phenol **163** was treated with phenyl boronic acid, methyl glyoxylate, and catalytic trichloroacetic acid according to the procedure of Nagata.[30] This reaction provided an inseparable mixture of diastereomeric alcohols **165** (dr = 4:3), the

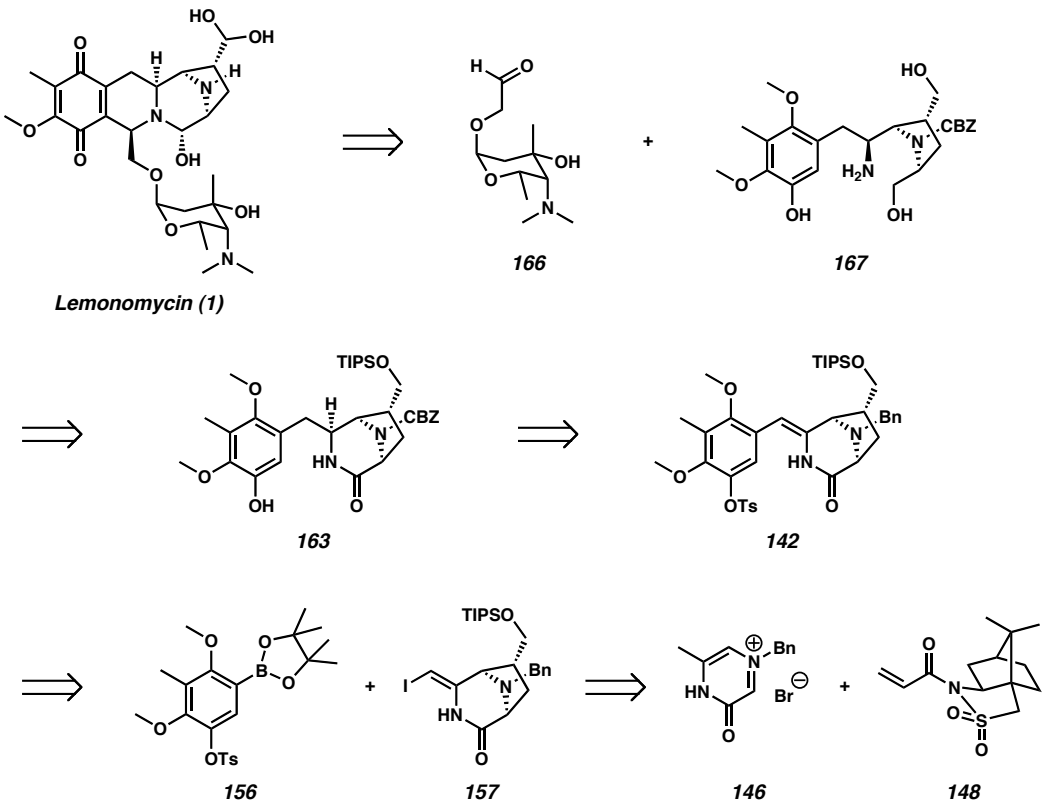
structures of which were assigned by ^{1}H NMR and mass spectral data. Unfortunately, cyclization of this compound to tetrahydroisoquinoline **164b** could not be induced under protic or Lewis acidic conditions, nor by conversion of the alcohol to a better leaving group.[31]

2.4 Final Synthetic Approach to (–)-Lemonomycin

Final Synthetic Plan

The failure of phenol **163** to cyclize to the tetrahydroisoquinoline was likely due to insufficient nucleophilicity of the amide nitrogen. To solve this problem, we altered our retrosynthetic analysis of lemonomycin to incorporate a Pictet-Spengler cyclization with primary amine **167** as its substrate (Scheme 2.13).[32] We also made a strategic decision to incorporate the lemonose unit on the aldehyde substrate (**166**), thus avoiding late stage glycosylation and protecting group manipulations. Aminotriol **167** would arise by reduction and silyl ether cleavage from tricycle **163**, the synthesis of which had already accomplished.

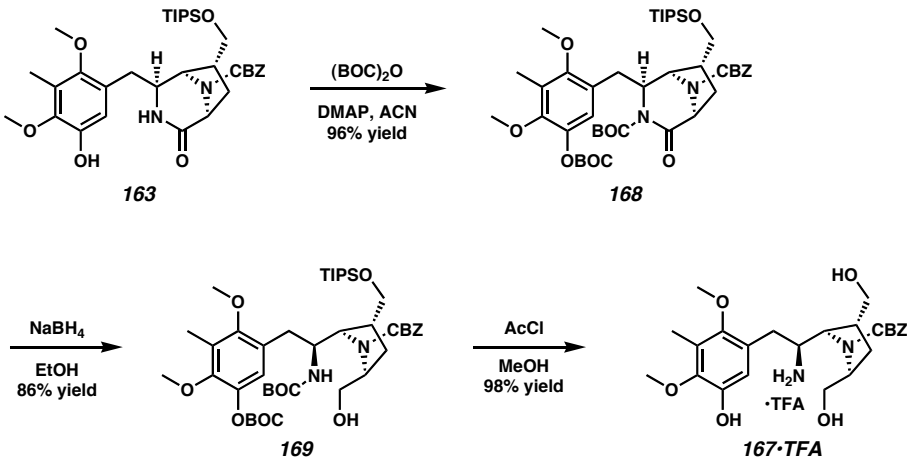
Scheme 2.13 Final Retrosynthetic Analysis of (–)-Lemonomycin



Synthesis of the Aminotriol

Due to the difficulty of direct reduction of amides to amino alcohols, lactam **163** was activated by conversion to imide **168** (Scheme 2.14). Reduction of **168** with excess sodium borohydride in ethanol then cleaved the lactam to protected amino alcohol **169**. Treatment of this compound with in situ-generated methanolic hydrochloric acid effected cleavage of the silyl ether and both BOC groups to provide aminotriol **167**, which was isolated as the trifluoroacetate salt after preparative HPLC purification. In model Pictet-Spengler reactions with a variety of α-hydroxyacetaldehyde derivates, **167** typically generated diastereomerically pure tetrahydroisoquinoline products.[33]

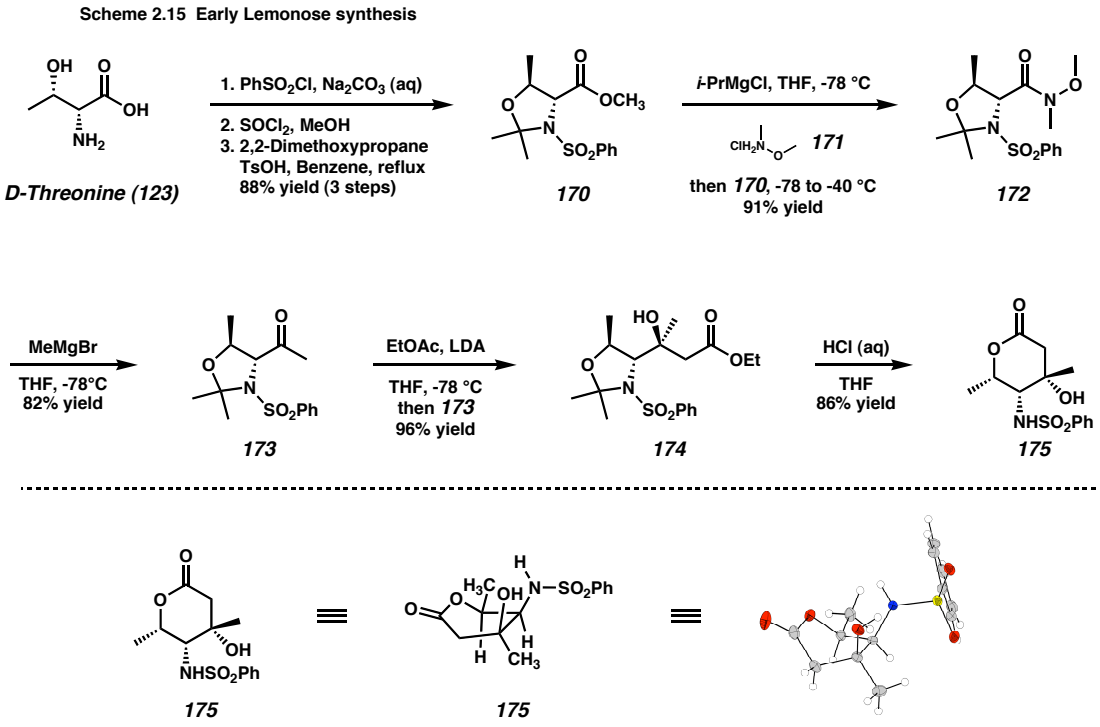
Scheme 2.14 Aminotriol Synthesis



Synthesis of Lemonose

With an effective amine substrate for the Pictet-Spengler reaction in hand, we began the synthesis of an aldehyde-appended lemonose fragment (i.e., **166**) as the Pictet-Spengler coupling partner.[34] After considering our two retrosynthetic analyses of lemonose (Scheme 2.2), we chose to pursue the better-precedented[5] route beginning with threonine. In this regard, D-threonine (**123**) was advanced to methyl ester **170** following known procedures (Scheme 2.15).[35,36] The methyl ester was converted to Weinreb amide **172** with the magnesium salt of *N,O*-dimethylhydroxylamine.[37] Treatment of **172** with methylmagnesium bromide cleanly yielded ketone **173**, which was expected to be an excellent substrate for Felkin-Ahn-controlled diastereoselective addition of nucleophiles.[38] Thus, addition of the lithium ketene acetal of ethyl acetate to ketone **173** generated tertiary alcohol **174** as a single diastereomer. Cleavage of the oxazolidine ring under acidic conditions proceeded with concomitant lactonization to provide lactone **175**, the relative stereochemistry of which was proven by X-ray diffraction analysis of a single crystal.[39]

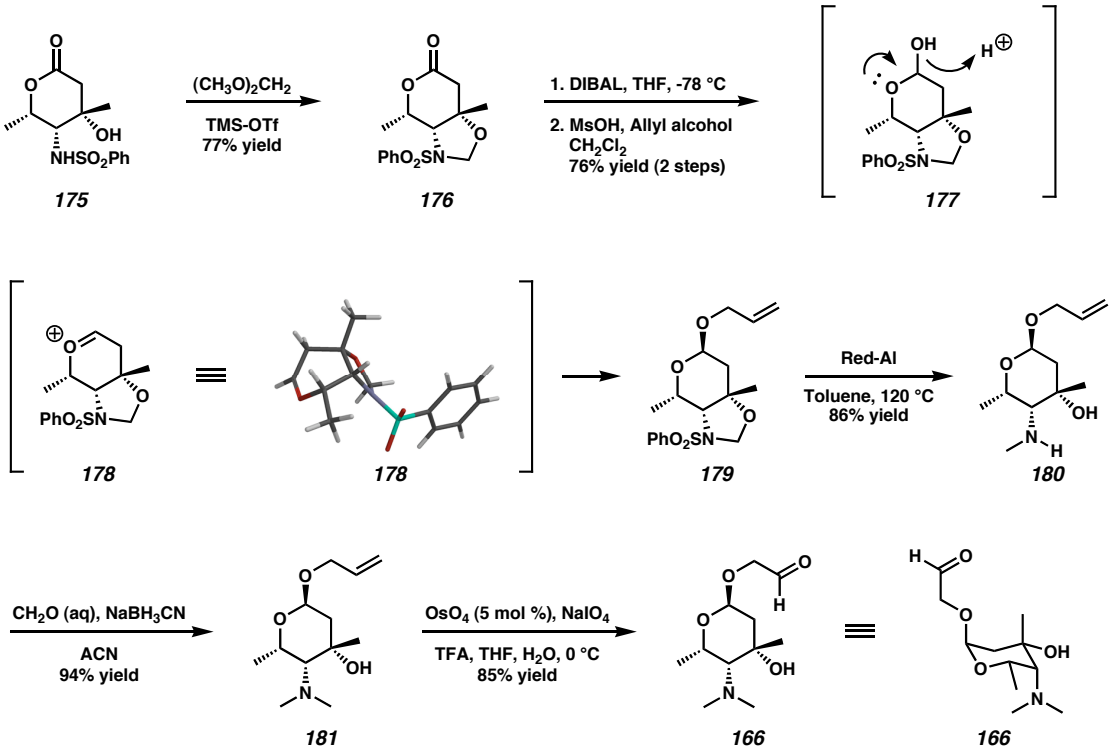
Scheme 2.15 Lemonose Synthesis: Preparation of a Key δ-Lactone



Lactone **175** was converted to oxazolidine **176** with dimethoxymethane and trimethylsilyl triflate (Scheme 2.16). The oxazolidine moiety served two important functions. First, the oxazolidine methylene acts as a latent methyl group for eventual conversion to the dimethylamine substituent. Second, the *cis*-fused bicyclic structure of oxazolidine **176** allowed for the highly diastereoselective introduction of an allyloxy group by reduction with DIBAL followed by treatment with allyl alcohol and methanesulfonic acid. Diastereoselectivity arose from the cup-shaped structure of intermediate oxocarbenium **178**.[40] Attack from the convex face of **178** provided allyl glycoside **179** with trace (<5%) amounts of the easily separable anomer.[41] Red-Al reduction removed the benzenesulfonyl group and cleaved the oxazolidine ring to yield secondary amine **180**, which was readily converted to the tertiary amine by reductive

methylation. Oxidative cleavage of the allyl group was then effected by catalytic dihydroxylation in the presence of sodium periodate, leading directly to glycosyloxy acetaldehyde **166**.[42]

Scheme 2.16 Synthesis of Lemonose

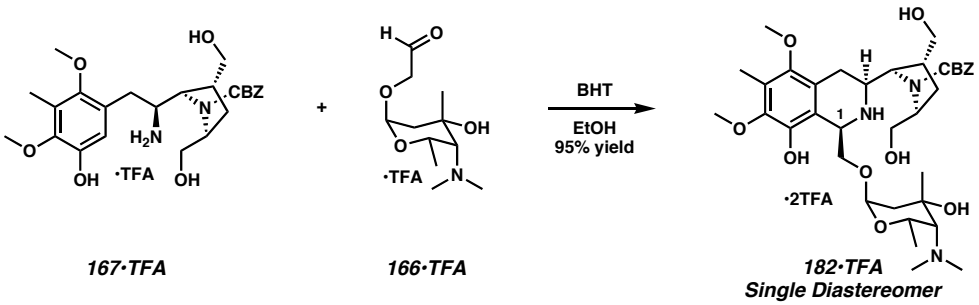


Completion of (–)-Lemonomycin

With the Pictet-Spengler substrates **166** and **167** in hand, we began the final campaign toward lemonomycin. To our delight, we discovered that simply mixing the trifluoroacetate salts of **166** and **167** in ethanol at room temperature provided 95% yield of tetrahydroisoquinoline **182** as a single diastereomer at C(1) (Scheme 2.17).[43] This reaction marked one of the first examples of a Pictet-Spengler cyclization employing a complex α-glycosyloxy aldehyde as a substrate.[44] The high yielding and completely

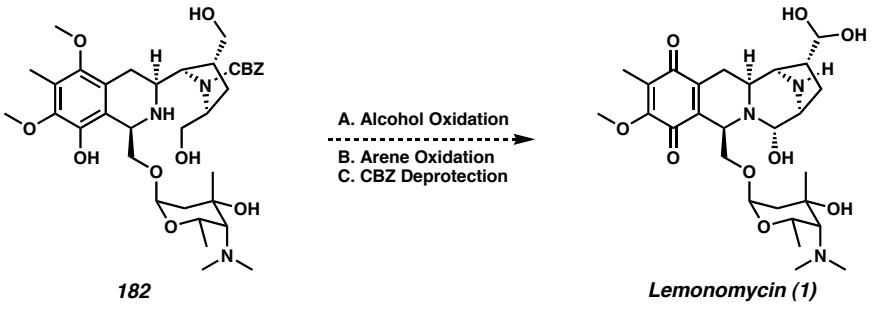
diastereoselective reaction also accomplished a highly convergent strategy for the synthesis of the lemonomycin core structure.

Scheme 2.17 Pictet-Spengler Cyclization



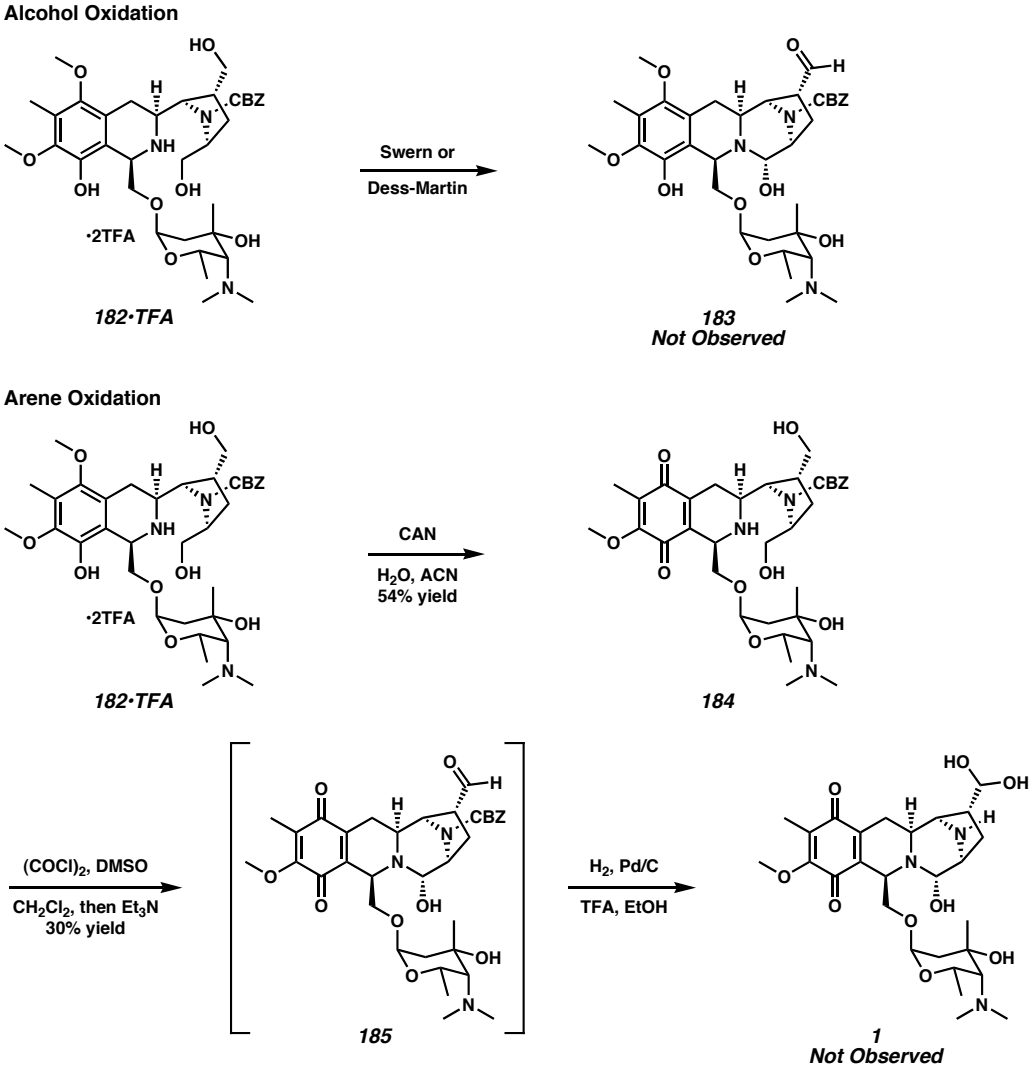
The remaining challenges for converting tetrahydroisoquinoline **182** to lemonomycin were threefold and deceptively simple (Scheme 2.18). The oxidation of the phenol to a quinone was required. The two alcohols were to be oxidized to the carbinolamine and aldehyde hydrate, respectively. It was expected that the two alcohol oxidations would be accomplished in a single reaction. Lastly, the carbamate protecting group had to be removed.

Scheme 2.18 Endgame Challenges



We first attempted to advance **182** by alcohol oxidation, but standard conditions for conversion to the bisaldehyde (Swern oxidation, Dess-Martin periodinane, etc.) failed on this compound (Scheme 2.19). We then tried the aromatic oxidation as the first of the three steps. This oxidation was achieved with ammonium cerium(IV) nitrate, yielding quinone **184** in moderate yield. Alcohol oxidation then was accomplished under Swern oxidation conditions, providing a compound with ^{1}H NMR and mass spectral data consistent with alcohol **185**.[45] Unfortunately, attempts to remove the CBZ group under hydrogenolytic or acidic conditions generated an array of unidentifiable decomposition products.

Scheme 2.19 Alcohol and Arene Oxidation Routes



Faced with the difficulties of routes beginning with either of the oxidations, we decided to first remove the CBZ group (Scheme 2.20). Thus, hydrogenolysis of **182** provided triaminotetraol **186** in good yield. Ammonium cerium (IV) nitrate oxidation then yielded quinone **187**, again bringing us within a single step of the natural product. Unfortunately, alcohol oxidation utilizing Dess-Martin periodinane,[46] Swern, Moffatt,

DMS/NBS,[47] Uemura,[48] Larock,[49] pyridinium dichromate, or TPAP/NMO[50] failed to yield even a trace of lemonomycin (**1**).

We therefore turned to the only path still available, which would require alcohol oxidation of triaminotetraol **186**. Despite the presence of confounding functionality in the form of the phenol, tertiary alcohol, and two secondary amines, we discovered that carefully controlled Swern oxidation conditions with DMSO present in cosolvent quantities effected the oxidation of **186** (Scheme 2.20). The oxidation was complicated by the formation of intermediate methylthiomethyl ether or amine groups,[51] but this problem was mitigated by treatment of the crude reaction mixture with aqueous hydrochloric acid, yielding clean phenol **188** in 52% yield along with two monooxidized compounds in 33% and 13% yield.[52] The completion of the synthesis was then accomplished by cerium(IV) oxidation of the phenol to provide (–)-lemonomycin. Our synthetic sample was identical to a natural sample by all spectroscopic and chromatographic methods, including ^{1}H NMR, ^{13}C NMR, IR, UV/Vis, HRMS, optical rotation, TLC, and HPLC coinjection.[53]

Scheme 2.20 Completion of (–)-Lemonomycin

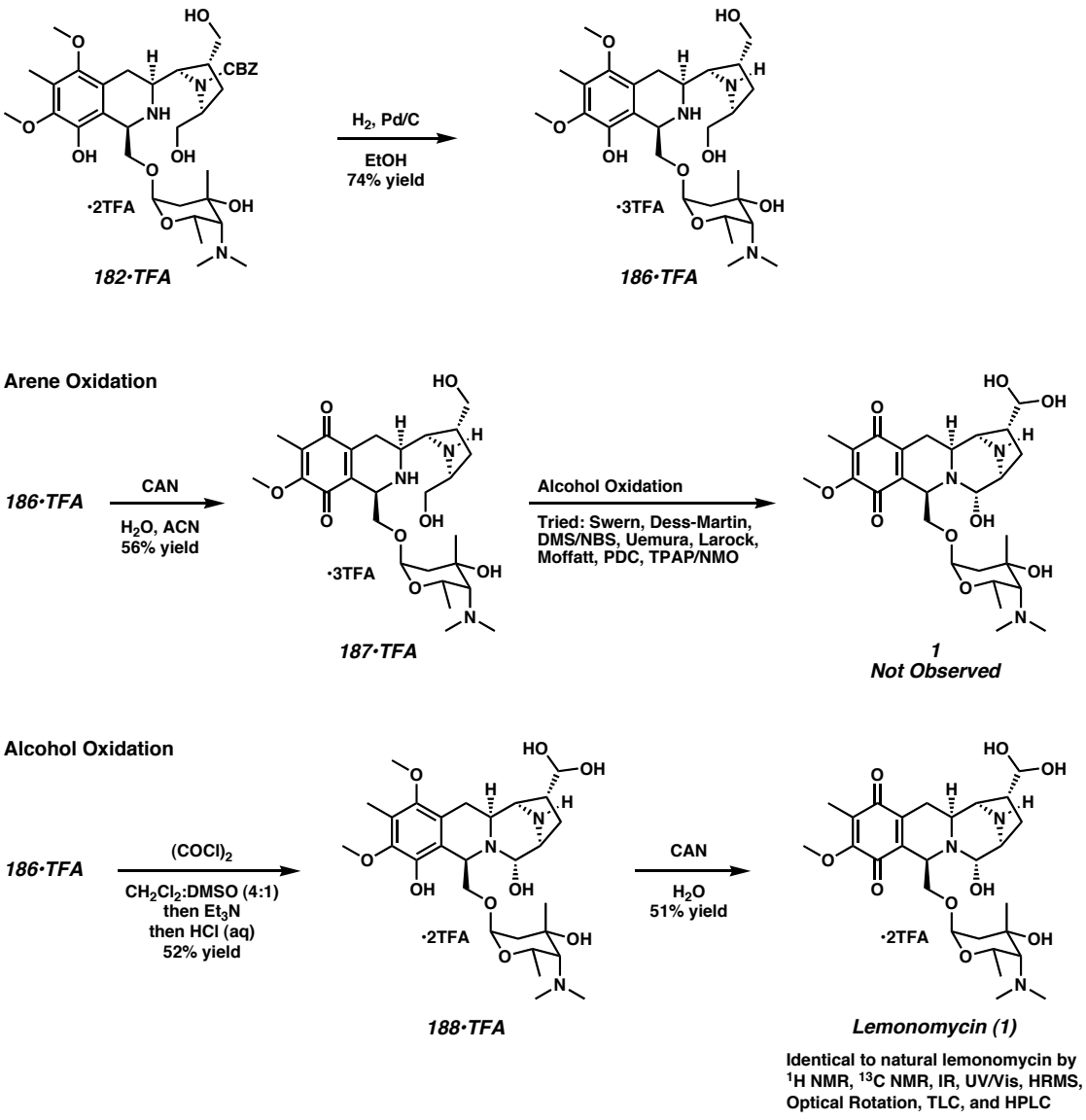
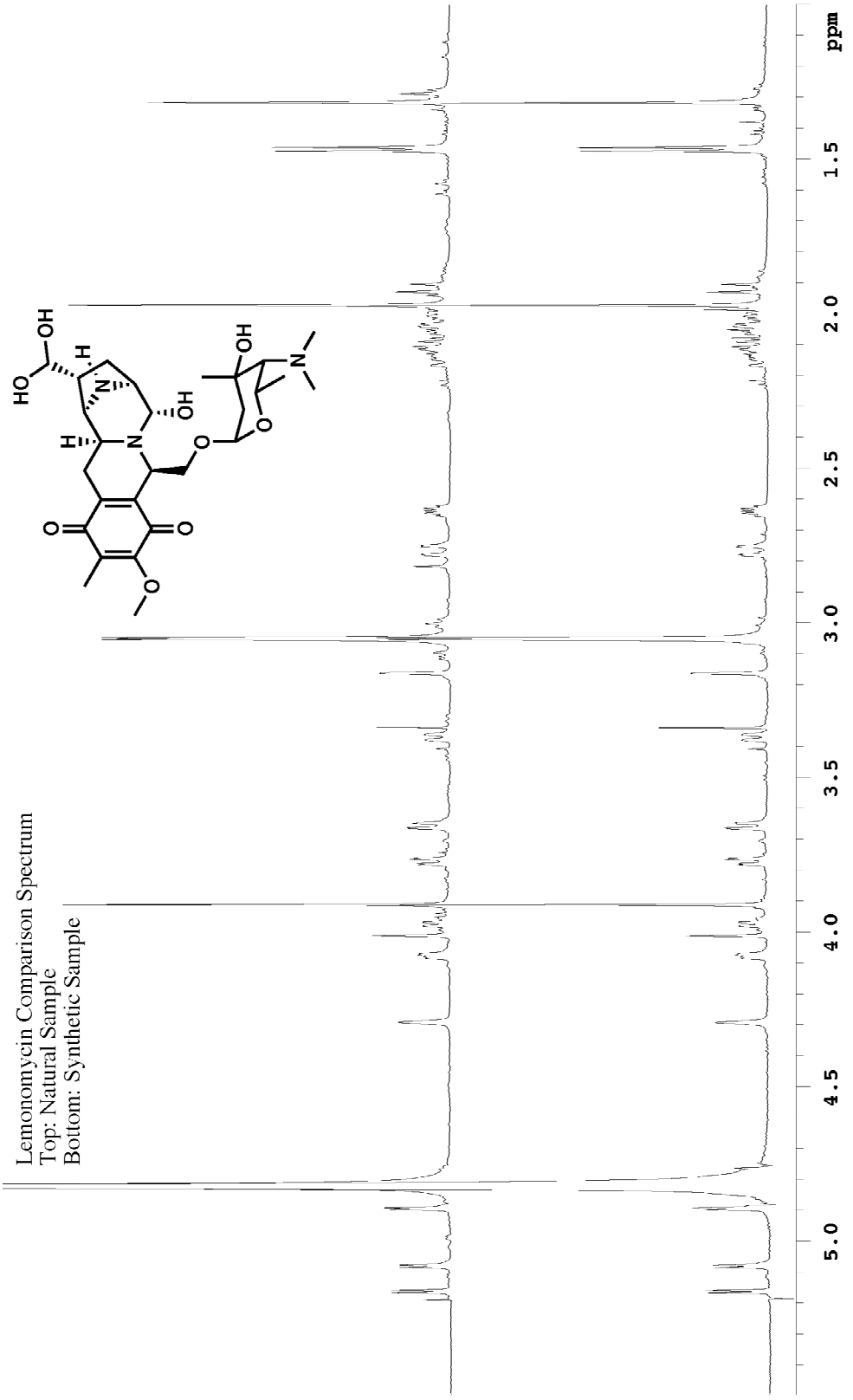


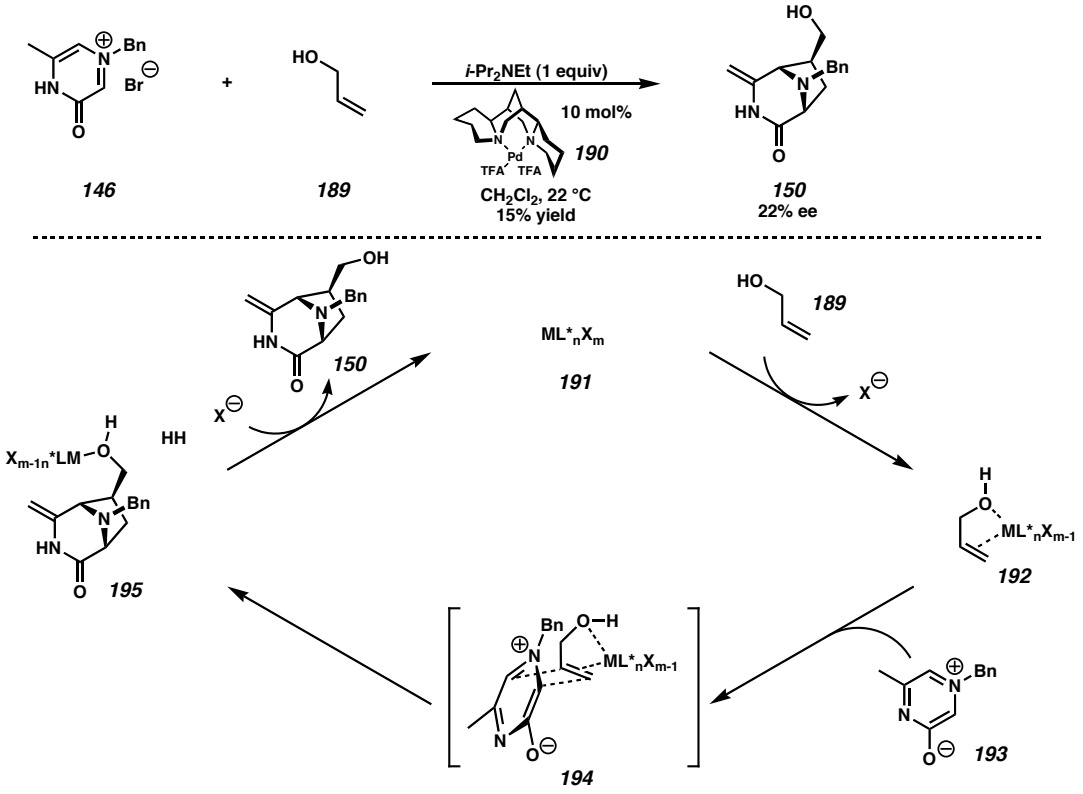
Figure 2.1 Comparison ^{1}H NMR Spectra of Natural and Synthetic (–)-Lemonomycin



2.5 Progress Toward a Catalytic Asymmetric Dipolar Cycloaddition

The reaction of oxidopyrazinium **146** with acrylamide **148** (Scheme 2.8) provided a route to enantiopure (–)-lemonomycin. While highly effective, this reaction required the use of a chiral auxiliary to induce asymmetry. A potentially more efficient and cost effective method of generating enantioenriched **150** would be the cycloaddition of **146** with allyl alcohol (**189**) catalyzed by a high oxidation state late transition metal coordinated by chiral ligands (e.g., **191**, Scheme 2.21).[54,55] We expected that this reaction would proceed mechanistically by π-coordination of allyl alcohol to the catalyst, producing intermediate **192**. It was hoped that the influence of the chiral ligands would cause the metal to bind only one prochiral face of the olefin. The LUMO of the bound olefin should be lowered relative to free allyl alcohol, such that the dipole will react selectively with complex **192**.[56] Cycloaddition onto the olefin face opposite from the metal catalyst through transition state **194** would produce bound diazabicycle **195**, which would dissociate to form enantioenriched **150** and the free metal catalyst.

Scheme 2.21 Catalytic Asymmetric Dipolar Cycloaddition



We first attempted the catalytic asymmetric cycloaddition of **146** with allyl alcohol in the presence of (–)-sparteine $Pd(TFA)_2$ complex **190**. We were pleased to find that these initial conditions provided diazabicycle **150** in 15% yield and 22% ee. Unfortunately, attempts to optimize this reaction by employing alternative ligands (diamines, bisphosphines, phosphinooxazolines,[57] pyridine/amidine ligands,[58] phenol/ oxazoline ligands,[59] and dienes[60]), metals ($NiBr_2$, $Pd(OAc)_2$, $PdCl_2$, $PdBr_2$, $PtCl_2$, PtI_2, $CuCl_2$, $CuBr_2$, $ZnCl_2$, $ZnBr_2$, $RhCl_3$, $IrCl_3$, and $RuCl_3$), bases, and solvents, as well as allyl ethers in place of allyl alcohol, provided no increase in either yield or enantioselectivity.

2.6 Concluding Remarks

The first total synthesis of (–)-lemonomycin has been accomplished in an efficient and highly convergent manner. Our synthetic planning evolved significantly during the project. Our original plan featured a Negishi coupling, subsequent dipolar cycloaddition, and a proposed amide Pictet-Spengler cyclization. After making significant progress along this route, we discovered a highly diastereoselective, auxiliary controlled dipolar cycloaddition with a simple dipole precursor. We therefore altered our synthetic plan to include this reaction followed by a key Suzuki coupling reaction and a diastereoselective enamide hydrogenation. After completing this hydrogenation, our planning was confounded by the poor reactivity of the resulting lactam. We circumvented this problem by reducing the lactam to a primary amine, which proved to be an excellent substrate for the unprecedented, highly convergent, high yielding, and completely diastereoselective Pictet-Spengler cyclization with the lemonose appended hydroxyacetaldehyde. Advancement of the Pictet-Spengler product to (–)-lemonomycin then was accomplished in three steps that notably only succeeded in the order of deprotection, alcohol oxidation, and final arene oxidation. The synthesis contains thirty-five total reactions from commercially available materials. The longest linear sequence is seventeen steps, counted from either glycinamide hydrochloride or D-threonine. The total yield of (–)-lemonomycin is 1.2% from glycinamide hydrochloride and 4.1% from D-threonine.

With the completion of the total synthesis of (–)-lemonomycin, the major goal of this project has been accomplished. Two areas of research, however, could warrant further attention. First, the synthesis of lemonose from D-threonine, though effective, is somewhat lengthy. A much shorter synthesis might be achieved if efficient and

enantioselective conditions can be developed for the hetero-Diels-Alder reaction proposed in Scheme 2.2. Second, our synthesis of lemonose has been applied to both enantiomeric series, thus providing (+)-*O*-oxoethyl-lemonose in addition to the (–)-*O*-oxoethyl-lemonose utilized for the synthesis (–)-lemonomycin. Use of (+)-*O*-oxoethyl-lemonose in an analogous Pictet-Spengler cyclization followed by the deprotection and oxidation steps would lead to a diastereomer of lemonomycin that might have improved biological activity. In a broader investigation, this strategy could be used for the incorporation of many different glycosyl units into the lemonomycin structure, leading to a library of potential antineoplastic agents and antibiotics with improved efficacy against highly resistant strains.

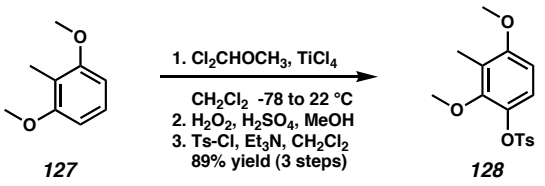
2.7 Experimental Procedures

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. Preparatory reversed-phase HPLC was performed on a Waters HPLC with a Waters Delta-Pak 25 x 100 mm, 15 μm C_{18} column equipped with a guard, utilizing a flow rate of 10 mL/min and a ramp of 1% B/min (A eluent = 95:5:0.05 water:acetonitrile:trifluoroacetic acid, B eluent = 5:95:0.01 water:acetonitrile:trifluoroacetic acid) with visualization at 270 nm. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a chiralcel AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd., with visualization at 254 nm. 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



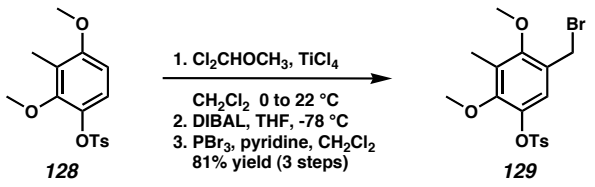
127 *128*

Tosyl Arene 128

To a –78 °C solution of 2,6-dimethoxytoluene (10.0 g, 65.7 mmol) and dichloromethyl methyl ether (7.7 mL, 85.4 mmol) in dichloromethane (65.7 mL) was added titanium tetrachloride (14.4 mL, 131 mmol) dropwise over 5 min. The reaction mixture was warmed to 20 °C over 30 min. The reaction mixture was then poured onto crushed ice (approximately 50 mL). After the ice had thawed, the mixture was extracted with dichloromethane (2 x 200 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude aldehyde (11.35 g, 96% yield).

To a solution of the crude aldehyde (11.35 g, 63 mmol) in methanol (90 mL) were added hydrogen peroxide (30% w/w in water, 9.3 mL, 82.0 mmol) and sulfuric acid (875 μL, 15.75 mmol). After 10 min, the reaction was quenched into a mixture of saturated aqueous sodium bicarbonate (100 mL) and water (100 mL). The mixture was extracted into dichloromethane (2 x 250 mL). The combined organics were dried over sodium sulfate and concentrated to yield the crude phenol (10.55 g, 97% yield).

To a solution of the phenol (10.15 g, 60.4 mmol) in dichloromethane (60 mL) were added triethylamine (8.4 mL, 60.4 mmol) and *p*-toluenesulfonyl chloride (11.5 g, 60.4 mmol). The reaction mixture was maintained at 20 °C for 3.5 h, after which acetonitrile (80 mL) and saturated aqueous sodium bicarbonate (50 mL) were added. After an additional hour the volatiles were removed in vacuo, and the residue was diluted with water (350 mL) and extracted into dichloromethane (2 x 250 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes eluent) to provide **128** (18.64 g, 96% yield) as a white solid. Alternatively, **128** could be obtained directly by recrystallization from ether with hexanes: R_F 0.67 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 9.3 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.43 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 151.2, 145.1, 136.4, 133.2, 129.6, 128.4, 121.4, 120.4, 105.2, 60.9, 55.8, 21.9, 9.3; IR (NaCl/film) 2941, 1597, 1483, 1371, 1177, 1111 cm^{-1}; HRMS (FAB) calc'd for $[C_{16}H_{18}O_5S+H]^+$: *m/z* 323.0953, found 323.0965.



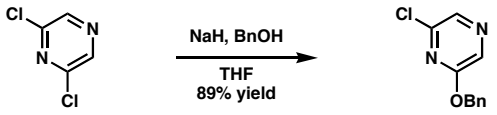
Benzylic Bromide 129

To a 0 °C solution of **128** (12.2 g, 37.8 mmol) and dichloromethyl methyl ether (6.8 mL, 75.7 mmol) in dichloromethane (75 mL) was added titanium tetrachloride (12.5 mL, 113.6 mmol). The solution was allowed to warm to 22 °C for 3 h, after which the reaction was quenched into ice water (500 mL). The mixture was extracted into dichloromethane (2 x 250 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude aldehyde (13.22 g, 99.7% yield).

To a –78 °C solution of the aldehyde (13.22 g, 37.7 mmol) in tetrahydrofuran (75 mL) was added DIBAL (8.07 mL, 45.3 mmol) dropwise over 5 min. The reaction mixture was maintained at –78 °C for 15 min, after which additional DIBAL (3.35 mL, 18.9 mmol) was added. After an additional 15 min, aqueous sodium potassium tartrate (200 mL) was added. The reaction mixture was allowed to warm to 22 °C with vigorous stirring for 1.5 h. The mixture was extracted with diethyl ether (3 x 200 mL). The combined organics were dried over magnesium sulfate and concentrated to provide the crude alcohol (13.05 g, 98% yield).

To a 0 °C solution of the alcohol (13.05 g, 37.1 mmol) and pyridine (2.99 mL, 37.1 mmol) in dichloromethane (37 mL) was added a solution of phosphorus tribromide (2.99 mL, 31.5 mmol) in dichloromethane (37 mL) dropwise over 7 min. After 10 min, the reaction mixture was filtered through silica gel with dichloromethane. The filtrate

was concentrated to yield analytically pure bromide **129** (12.65 g, 82.5% yield) as a white powder: R_F 0.55 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.88 (s, 1H), 4.43 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.46 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 152.5, 145.6, 138.9, 133.1, 129.9, 128.7, 127.2, 126.9, 122.9, 61.3, 61.1, 27.8, 21.9, 10.1; IR (NaCl/film) 2943, 1598, 1482, 1374, 1191, 1177, 991, 843, 769 cm^{-1}; HRMS (FAB+) calc'd for $[C_{17}H_{19}O_5SBr]^{\bullet+}$: *m/z* 414.0136, found 414.0145.

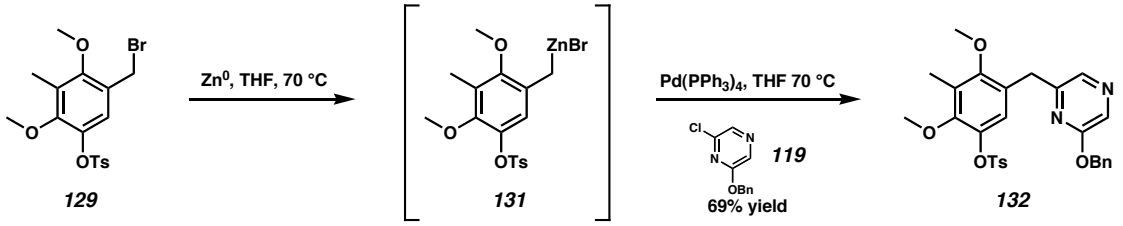


130 *119*

Chloropyrazine 119

To a suspension of sodium hydride (60% suspension in mineral oil, 1.47 g, 36.85 mmol) in tetrahydrofuran (67 mL) was added benzyl alcohol (3.47 mL, 33.56 mmol) (caution: hydrogen evolution). After 15 min, 2,6-dichloropyrazine (5.0 g, 33.56 mmol) was added in portions over 5 min (caution: exotherm). After 5.5 h, the reaction mixture was diluted with diethyl ether (250 mL) and washed with water (250 mL) followed by saturated aqueous sodium chloride (100mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (3:97 to 7:93 ethyl acetate:hexanes eluent) to provide **119** as a white solid: R_F 0.38 (10:90 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.17 (s, 1H), 7.48-7.35 (comp m, 5H), 5.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 145.6, 135.7, 135.6,

133.5, 128.8, 128.7, 128.6, 69.1; IR (NaCl/film) 1565, 1523, 1408, 1361, 1305, 1175, 1002 cm^{-1}; HRMS (EI+) calc'd for $[C_{11}H_9N_2OCl]^{\bullet+}$: *m/z* 220.0403, found 220.0408.



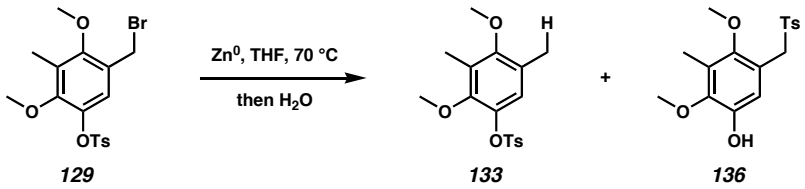
Bisarene 132

The yield of this reaction varied unpredictably from trial to trial. The following procedure is a representative example.

To a suspension of zinc dust (1.57 g, 24 mmol) in THF (4 mL) was added ethereal hydrogen chloride (2 M, 60 μL, 120 μmol). After 20 min, the mixture was cooled to –78 °C and evacuated to 1 torr for 20 min to effect deoxygenation. The suspension was then heated to reflux.

To the refluxing suspension of zinc dust was added a degassed solution of bromide **129** (500 mg, 1.20 mmol) in tetrahydrofuran (4 mL) via cannula. After 10 min, the reaction mixture was cooled to 22 °C and passed through a schlenk filter into a solution of chloropyrazine **119** (265 mg, 1.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (69 mg, 60 μmol) in tetrahydrofuran (4 mL). The reaction mixture was heated to reflux for 5 h, cooled to 22 °C, and diluted with water (100 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80 to 25:75 ethyl acetate:hexanes eluent) to provide

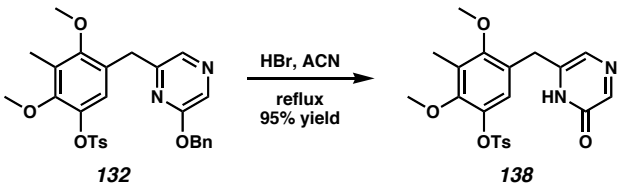
bisarene **132** (430.5 mg, 69% yield) as an off-white foam: R_F 0.25 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.94 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.42-7.31 (comp m, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.84 (s, 1H), 5.34 (s, 2H), 3.96 (s, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 2.42 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4155.9, 152.0, 150.6, 145.3, 138.9, 136.6, 135.8, 133.4, 133.3, 129.7, 128.6, 128.5, 128.4, 128.2, 127.3, 126.7, 122.6, 67.9, 61.0, 60.9, 34.9, 21.8, 10.1; IR (NaCl/film) 2941, 1536, 1482, 1416, 1371, 1191, 1177, 1008 cm^{-1}; HRMS (FAB+) calc'd for $[C_{28}H_{28}N_2O_6S+H]^+$: *m/z* 521.1746, found 521.1722.



Toluene 133 and Phenol 136

To a refluxing suspension of zinc dust (653.7 mg, 10.0 mmol) in tetrahydrofuran (2.5 mL) was added ethereal hydrogen chloride (2 M, 25 μL, 50 μmol). After 10 min, a solution of bromide **129** (207.7 mg, 500 μmol) in tetrahydrofuran (2.5 mL) was added dropwise over 5 min. After an additional 10 min, the reaction was quenched with water (1 mL), cooled to 22 °C, diluted with diethyl ether (35 mL), and washed with water (50 mL) followed by saturated aqueous sodium chloride (25 mL). The organic layer was dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 30:70 ethyl acetate:hexanes eluent) to yield toluene **133** (59.7 mg, 36% yield) and phenol **136** (92.4 mg, 55% yield). Characterization of **133**: R_F 0.45

(30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.79 (s, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.45 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 149.6, 145.3, 138.7, 133.6, 129.8, 128.6, 126.9, 126.3, 122.5, 60.9, 60.1, 21.9, 16.0, 9.9; IR (NaCl/film) 2938, 1483, 1371, 1191, 1176, 1022, 844, 570, 551 cm^{-1}; HRMS (EI+) calc'd for $[C_{17}H_{20}O_5S]^{\bullet+}$: *m/z* 336.1031, found 336.1027. Characterization of **136**: R_F 0.18 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.97 (s, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 152.3, 145.6, 138.8, 133.3, 129.9, 128.6, 127.1, 124.8, 122.9, 73.8, 62.0, 61.0, 21.9, 9.9; IR (NaCl/film) 3439 (br), 2943, 1483, 1371, 1191, 1176, 1110, 551 cm^{-1}; HRMS (EI+) calc'd for $[C_{17}H_{20}O_5S\text{-}H]^+$: *m/z* 335.0953, found 335.0946.

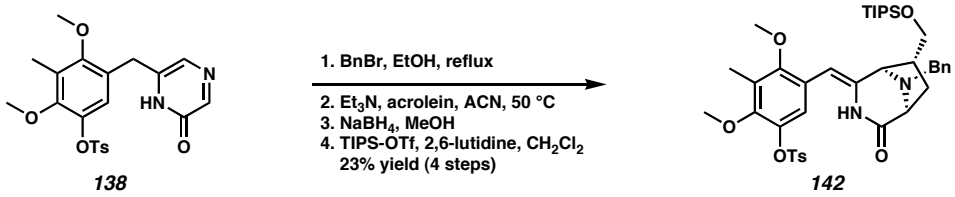


132 *138*

Pyrazinone 138

To a solution of pyrazine **132** (200 mg, 384 μmol) in acetonitrile (3.8 mL) was added aqueous hydrobromic acid (870 μL, 7.68 mmol). The reaction mixture was heated to reflux for 1 h, cooled to 22 °C, and quenched into a solution of saturated aqueous sodium bicarbonate (40 mL), saturated aqueous sodium thiosulfate (3 mL), and water (30 mL). The mixture was extracted with ethyl acetate (2 x 35 mL). The combined organics

were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:100 to 2:98 methanol:chloroform eluent) to yield pyrazinone **138** (156.8 mg, 95% yield) as a light yellow plastic: R_F 0.43 (50:50 acetone:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (br s, 1H), 8.00 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 1H), 6.85 (s, 1H), 3.75 (s, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.44 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.8, 151.7, 146.7, 145.6, 139.11, 139.10, 133.2, 129.9, 128.5, 127.3, 124.3, 123.7, 122.5, 61.0, 31.5, 21.9, 10.3; IR (NaCl/film) 2934, 1656, 1607, 1481, 1372, 1177, 994 cm^{-1}; HRMS (FAB+) calc'd for $[C_{21}H_{22}N_2O_6S+H]^+$: *m/z* 431.1277, found 431.1281.



138 *142*

Diazabycycle 142 from Pyrazinone 138

To a solution of pyrazinone **138** (343.5 mg, 799 μmol) in anhydrous ethanol (4 mL) was added benzyl bromide (925 μL, 7.99 mmol). The reaction mixture was heated to reflux for 20 h, cooled to 22 °C, concentrated to approximately 1 mL volume, and filtered through silica gel (0:100 to 20:80 methanol:chloroform eluent). Fractions containing the oxidopyrazinium (R_F 0.05, 5:95 methanol:chloroform) were concentrated to a violet oil that was used immediately.

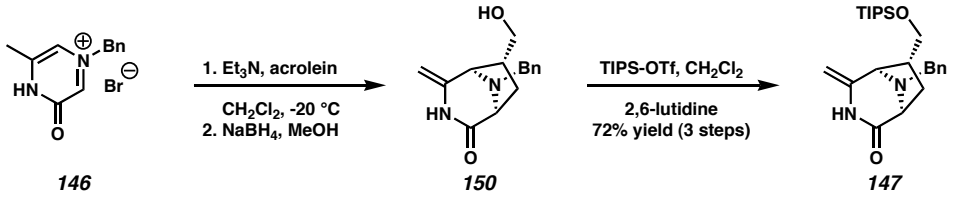
To a 50 °C solution of the oxidopyrazinium in acetonitrile (4 mL) were added triethylamine (122 μL, 879 μmol) and acrolein (59 μL, 879 μmol). After 2 h, the

reaction mixture was cooled to 22 °C, diluted with water (50 mL), and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude cycloadducts.

To a solution of the crude cycloadducts in methanol (8 mL) was added sodium borohydride (303 mg, 7.99 mmol) in portions over 10 min. After an additional 10 min, hydrochloric acid (1 M in water, 15 mL) was added. After an additional 10 min, the mixture was diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and concentrated to yield the crude alcohols.

To a solution of the crude mixture of alcohols in dichloromethane (8 mL) were added 2,6-lutidine (102 μL, 879 μmol) and triisopropylsilyl trifluoromethanesulfonate (236 μL, 879 μmol). After 1 h, additional 2,6-lutidine (46.4 μL, 400 μmol) and triisopropylsilyl trifluoromethanesulfonate (107 μL, 400 μmol) were added. After an additional 30 min, the reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80 ethyl acetate:hexanes eluent) to provide diazabicyle **142** (135.5 mg, 23% yield) as a yellow oil: R_F 0.37 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.35-7.19 (comp m, 7H), 6.75 (s, 1H), 5.17 (s, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.72-3.58 (comp m, 4H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.35 (m, 1H), 2.14 (s, 3H), 2.09 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.69 (ddd, *J* = 12.6, 7.2, 6.0 Hz, 1H), 1.01 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.9, 150.6, 145.5, 139.2, 138.3, 137.4, 135.1, 133.4, 129.9, 128.9, 128.6, 127.6,

127.5, 123.8, 122.2, 100.2, 66.0, 63.8, 62.8, 61.2, 60.3, 52.8, 47.4, 32.6, 22.1, 18.4, 12.3, 10.2; IR (NaCl/film) 2942, 2865, 1694, 1661, 1378, 1178, 1110, 993, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{54}N_2O_7SSi+H]^+$: *m/z* 735.3499, found 735.3508.



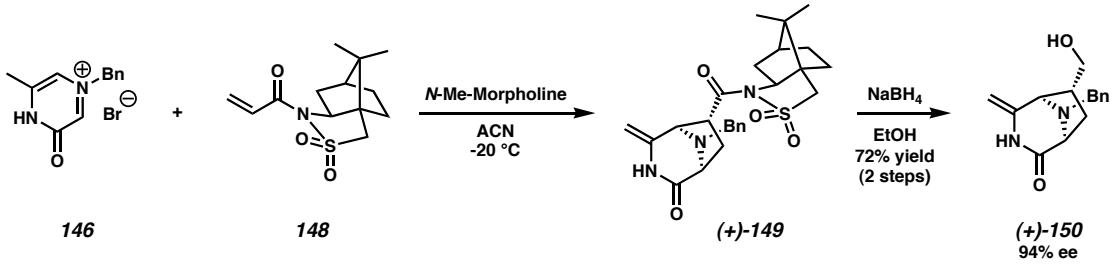
146 *150* *147*

Silyl Ether 147 by Racemic Dipolar Cycloaddition

To a suspension of oxidopyrazinium bromide **146** (10.0 g, 35.6 mmol) in dichloromethane (119 mL) was added triethylamine (14.9 mL, 107 mmol), affording a clear solution that was cooled to -20 °C over 15 min. Acrolein (7.15 mL, 107 mmol) was then added dropwise over 5 min. The reaction mixture was maintained at -20 °C for 74 h, then warmed to 0 °C and diluted with methanol (71 mL). Sodium borohydride (5.4 g, 142 mmol) was added in portions over 15 min. After an additional 15 min, the reaction mixture was warmed to room temperature, quenched with saturated aqueous ammonium chloride (200 mL) and water (300 mL), and extracted into dichloromethane (200 mL, 250 mL). The combined organics were dried over sodium sulfate, concentrated, and dried aziotropically from benzene (50 mL) to provide racemic **150**, which was used without further purification.

To a solution of crude **150** in dichloromethane (71 mL) were added 2,6-lutidine (4.57 mL, 39.2 mmol) and triisopropylsilyl trifluoromethanesulfonate (10.5 mL, 39.2 mmol). After 75 min the reaction was quenched with water (500 mL) and extracted into

dichloromethane (100 mL, 150 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 ethyl acetate:hexanes eluent) to provide racemic **147** (10.65 g, 72% yield) as a white solid: R_F 0.41 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (comp m, 6H), 4.21 (s, 1H), 4.08 (s, 1H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 1H), 3.63-3.54 (comp m, 2H), 3.51 (d, *J* = 6.9 Hz, 1H), 2.34 (app ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H), 2.09 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.69 (ddd, *J* = 13.2, 7.2, 5.2 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 142.7, 138.4, 128.8, 128.3, 127.2, 90.6, 65.9, 63.2, 61.2, 52.5, 47.1, 32.3, 18.3, 12.2; IR (NaCl/film) 3195, 2943, 2866, 1687, 1650, 1105 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{38}N_2O_2Si+H]^+$: *m/z* 415.2781, found 415.2786.



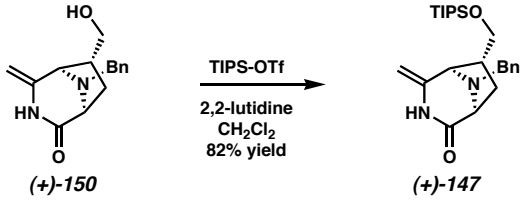
Diazabicycles (+)-149 and (+)-150

To a chilled (-20 °C) suspension of **146** (421.5 mg, 1.5 mmol) in acetonitrile (15 mL) were added **148** (485 mg, 1.8 mmol) and *N*-methylmorpholine (495 μL, 4.5 mmol), affording a clear solution. The reaction mixture was maintained at -20 °C for 72 h, after which ethanol (15 mL) and sodium borohydride (570 mg, 15 mmol) were added. The reaction mixture was warmed to 20 °C for 4.5 h, after which additional sodium

borohydride (570 mg, 15 mmol) was added. After an addition 1.5 h the reaction was quenched with saturated aqueous ammonium chloride (125 mL) and extracted with ethyl acetate (100 mL, 50 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (40:60 to 85:15 ethyl acetate:hexanes eluent) to provide **(+)-150** (278 mg, 72% yield, 94.7% ee) as a colorless oil: R_F 0.11 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.38-7.25 (comp m, 5H), 4.32 (d, *J* = 1.2 Hz, 1H), 4.15 (br s, 1H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.73 (m, 1H), 3.72 (d, *J* = 12.9 Hz, 1H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.57 (m, 1H), 3.56 (s, 1H), 2.81 (br s, 1H), 2.37 (m, 1H), 2.21 (dd, *J* = 12.9, 9.0 Hz, 1H), 2.09 (ddd, *J* = 13.2, 7.3, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 141.7, 137.7, 129.0, 128.7, 127.8, 91.2, 66.2, 63.2, 63.0, 52.6, 45.5, 32.9; IR (NaCl/film) 3354, 3210, 2936, 1676, 1317 cm^{-1}; HRMS (FAB) calc'd for $[C_{15}H_{18}N_2O_2+H]^+$: *m/z* 259.1447, found 259.1457; $[\alpha]_D^{23}$ +44.2° (*c* 0.5, $CHCl_3$). HPLC analysis (Chiracel AD column, 10:90 2-propanol:hexanes, 1 mL/min, λ = 254 nm) showed the product to be of 94.7% ee (t_{fast} = 17.95 min, major; t_{slow} = 22.28 min, minor).

An analytical sample of the intermediate cycloadduct **(+)-149** was prepared by flash chromatography on silica gel (20:20:60 acetone:dichloromethane:hexanes eluent): R_F 0.33 (25:25:50 acetone:dichloromethane:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.32-7.22 (comp m, 5H), 4.37 (d, *J* = 1.2 Hz, 1H), 4.32 (d, *J* = 0.6 Hz, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.89 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.75 (br d, *J* = 7.2 Hz, 1H), 3.68 (br s, 1H), 3.59 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.41 (s, 2H), 3.06 (ddd, *J* = 13.2, 7.8, 3.9 Hz, 1H), 2.15 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.06 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.96-1.79 (comp m, 4H), 1.46-1.30 (comp m, 2H), 0.92 (s, 3H), 0.75 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 139.2, 138.1, 128.8, 128.5, 127.5, 93.8, 65.8, 63.4, 63.3, 53.3, 52.1, 49.1, 48.5, 47.9, 44.8, 38.5, 33.0, 31.3, 26.6, 20.7, 20.0; IR (NaCl/film) 3313, 3199, 2958, 1695, 1653, 1330, 1211, 1133 cm^{-1}; HRMS (FAB) calc'd for $[C_{25}H_{31}N_3O_4S+H]^+$: *m/z* 470.2114, found 470.2127; $[\alpha]_D^{25}$ +137.3° (*c* 0.5, acetone).

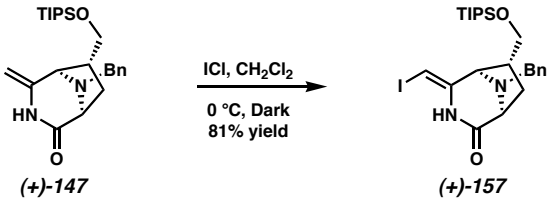


(+)-150 *(+)-147*

Silyl ether (+)-147

To a solution of **(+)-150** (1.9 g, 7.36 mmol) in dichloromethane (25 mL) were added 2,6-lutidine (1.03 mL, 8.83 mmol) and triisopropylsilyl trifluoromethanesulfonate (2.37 mL, 8.83 mmol). After 15 min, the reaction was quenched with water (150 mL) and extracted with dichloromethane (50 mL, 30 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 30:70 ethyl acetate:hexanes eluent) to provide **(+)-147** (2.50 g, 82% yield) as a colorless oil: R_F 0.41 (30:70 ethyl acetate:hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (comp m, 6H), 4.21 (s, 1H), 4.08 (s, 1H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 1H), 3.63-3.54 (comp m, 2H), 3.51 (d, *J* = 6.9 Hz, 1H), 2.34 (app ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H), 2.09 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.69 (ddd, *J* = 13.2, 7.2, 5.2 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 142.7, 138.4, 128.8, 128.3, 127.2, 90.6, 65.9, 63.2, 61.2, 52.5, 47.1, 32.3, 18.3, 12.2; IR (NaCl/film) 3195, 2943,

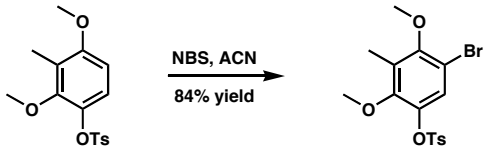
2866, 1687, 1650, 1105 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{38}N_2O_2Si+H]^+$: *m / z* 415.2781, found 415.2786; $[\alpha]_D^{23}$ +25.7° (*c* 1.5, acetone).



Iodoenamide (+)-157

(Note: reaction run in a foil-wrapped flask to exclude light.) To a cooled (0 °C) solution of **(+)-147** (10.65 g, 25.7 mmol) in dichloromethane (128 mL) was added a cooled (0 °C) solution of iodine monochloride (6.26 g, 38.6 mmol) in dichloromethane (38.6 mL) via cannula over 5 min. After 30 min, additional iodine monochloride (1.25 g, 7.7 mmol) in dichloromethane (7.7 mL) was added. After an additional 15 min, the reaction was quenched with saturated aqueous sodium bisulfite (100 mL) followed by saturated aqueous sodium bicarbonate (100 mL). After stirring vigorously for 15 min (caution: gas evolution) the reaction mixture was diluted with water (150 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (150 mL), and the combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 ethyl acetate:hexanes eluent) to provide **(+)-157** (11.32 g, 82% yield) as a colorless oil: R_F 0.65 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.33-7.24 (comp m, 5H), 4.98 (s, 1H), 3.85 (s, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.64-3.54 (comp m, 2H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.33 (m, 1H), 2.09 (dd, *J* = 13.2, 9.3 Hz, 1H),

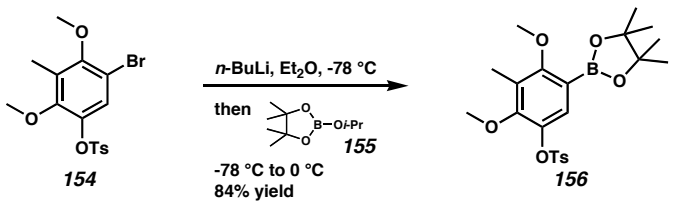
1.69 (ddd, J = 13.2, 7.2, 5.5 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 144.1, 137.7, 128.7, 128.5, 127.5, 65.7, 63.5, 62.8, 52.6, 46.6, 32.1, 18.3, 12.2; IR (NaCl/film) 2941, 2864, 1703, 1632, 1280, 1104, 683 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{37}IN_2O_2Si+H]^+$: m/z 541.1748, found 541.1755; $[\alpha]_D^{25}$ +47.3° (c 1.0, acetone).



128 *154*

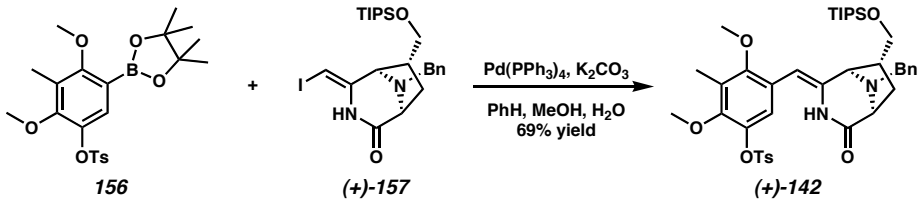
Aryl Bromide 154

To a solution of arene **128** (1.0 g, 3.1 mmol) in acetonitrile (10 mL) was added *N*-bromosuccinimide (580 mg, 3.2 mmol). After 10.5 h the reaction mixture was diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium bicarbonate (100 mL), dried over sodium sulfate, concentrated, and filtered through a pad of silica gel (30:70 ethyl acetate:hexanes eluent) to provide **154** (1.04 g, 84% yield) as a white solid: R_F 0.67 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.15 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 151.1, 145.6, 139.1, 132.9, 129.8, 128.5, 128.2, 124.7, 110.9, 61.1, 60.6, 22.0, 10.7; IR (NaCl/film) 2940, 1469, 1377, 1177, 554 cm^{-1}; HRMS (FAB) calc'd for $[C_{16}H_{17}BrO_5S+H]^+$: m/z 401.0058, found 401.0045.



Arylboronic ester 156

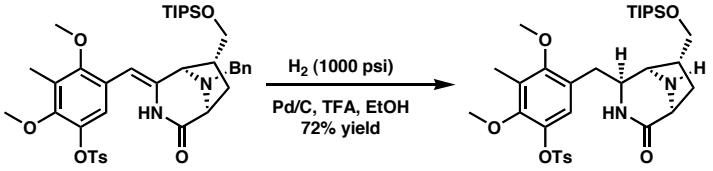
To a chilled (-78 °C) solution of **154** (2.5 g, 6.23 mmol) in anhydrous diethyl ether (62 mL) was added *n*-butyllithium (4.3 mL, 2.5M solution in hexanes, 10.9 mmol) dropwise over 5 min. After 20 min a solution of 2-isopropoxy-4,4,5,5-tetramethyldioxaborolane (**155**, 2.5 mL, 12.5 mmol) in anhydrous diethyl ether (41 mL) was added via cannula over 5 min. The reaction mixture was then warmed to -40 °C over 20 min and quenched with saturated aqueous ammonium chloride (50 mL). After warming to 20 °C, the mixture was diluted with water (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes eluent) to provide **156** (2.35 g, 84% yield) as a colorless oil: R_F 0.65 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.22 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.46 (s, 3H), 2.13 (s, 3H), 1.32 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 154.0, 145.0, 138.2, 133.0, 129.5, 128.3, 128.1, 126.2, 83.6, 62.1, 60.7, 24.8, 21.7, 9.5; IR (NaCl/film) 2979, 2935, 1597, 1358, 1178, 1143 cm^{-1}; HRMS (FAB) calc'd for $[C_{22}H_{29}BO_7S+H]^+$: m/z 449.1805, found 449.1819.



Styrene (+)-142

To a solution of aryl boronic ester **156** (3.1 g, 6.9 mmol) and iodoenamide **(+)-157** (3.75 g, 6.9 mmol) in benzene (138 mL) were added methanol (27.6 mL), aqueous potassium carbonate (2.0 M, 13.8 mL, 27.6 mmol) and tetrakis(triphenylphosphine)-palladium (399 mg, 345 μmol, 5 mol%). The reaction mixture was deoxygenated by twice freezing under vacuum, flushing with argon, and melting. The reaction mixture was then sealed under argon and heated to 70 °C for 3.5 h. The mixture was then cooled to 23 °C, diluted with water (50 mL) and saturated aqueous sodium chloride (50 mL), and extracted with ethyl acetate (100 mL) followed by dichloromethane (100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 20:80 ethyl acetate:hexanes eluent) to provide **(+)-142** (3.47 g, 69% yield) as a yellow oil: R_F 0.37 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.35-7.19 (comp m, 7H), 6.75 (s, 1H), 5.17 (s, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.72-3.58 (comp m, 4H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.35 (m, 1H), 2.14 (s, 3H), 2.09 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.69 (ddd, *J* = 12.6, 7.2, 6.0 Hz, 1H), 1.01 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.9, 150.6, 145.5, 139.2, 138.3, 137.4, 135.1, 133.4, 129.9, 128.9, 128.6, 127.6, 127.5, 123.8, 122.2, 100.2, 66.0, 63.8, 62.8, 61.2, 60.3, 52.8, 47.4, 32.6, 22.1, 18.4, 12.3, 10.2; IR (NaCl/film) 2942, 2865, 1694, 1661, 1378,

1178, 1110, 993, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{54}N_2O_7SSi+H]^+$: *m/z* 735.3499, found 735.3508; $[\alpha]_D^{25}$ +40.1° (*c* 0.5, acetone).

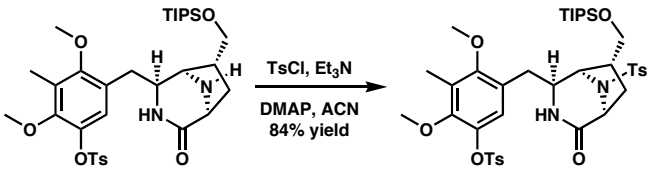


(+)-142 *(–)-158*

Lactam (–)-158

To an ethanol (58 mL) solution of **(+)-142** (2.13 g, 2.90 mmol) were added trifluoroacetic acid (4.5 mL, 58 mmol) and palladium on carbon (10% w/w, 4.26 g). The reaction mixture was pressurized to 1000 psi with hydrogen in a stainless steel reaction vessel for 28 h. The reaction mixture was then diluted with a mixture of water (175 mL), saturated aqueous sodium bicarbonate (175 mL), and saturated aqueous sodium chloride (175 mL), and extracted with ethyl acetate (150 mL, 2 x 100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:100 to 5:95 triethylamine:chloroform eluent) to provide **(–)-158** (1.345 g, 72% yield) and a colorless oil: R_F 0.52 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 5.30 (s, 1H), 3.79-3.68 (comp m, 6H), 3.67 (s, 3H), 3.59 (app q, *J* = 8.5 Hz, 1H), 3.47 (s, 1H), 2.69 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.63-2.49 (comp m, 2H), 2.47 (s, 3H), 2.23-2.04 (comp m, 2H), 2.15 (s, 3H), 1.62 (ddd, *J* = 12.8, 6.6, 6.6 Hz, 1H), 1.07 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 156.1, 150.9, 145.5, 138.9, 133.2, 129.9, 128.5, 127.3, 125.7, 122.2, 66.3, 61.0, 60.8, 60.3, 60.0, 58.8, 38.6, 35.2, 33.0, 22.1, 18.4, 12.2,

10.3; IR (NaCl/film) 2943, 2866, 1678, 1483, 1377, 1178, 1109, 1008 cm^{-1}; HRMS (FAB) calc'd for $[C_{33}H_{50}N_2O_7SSi+H]^+$: *m/z* 647.3186, found 647.3183; $[\alpha]_D^{23}$ -15.9° (*c* 1.0, acetone).

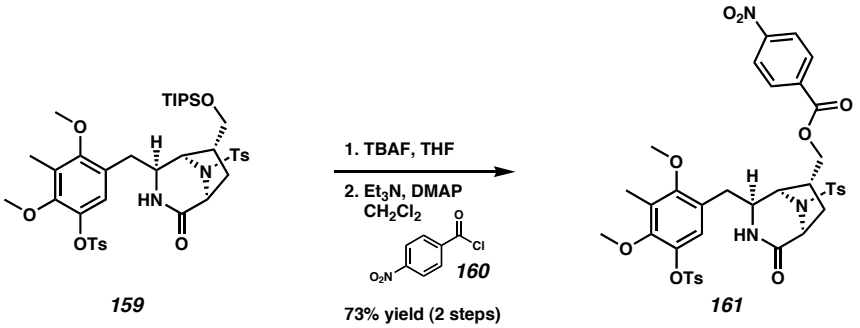


158 *159*

Tosamide 159

To a solution of **158** (200 mg, 310 μmol) in acetonitrile (6.2 mL) were added triethylamine (130 μL, 930 μmol), *N,N*-dimethylaminopyridine (19 mg, 155 μmol), and *p*-toluenesulfonyl chloride (88.7 mg, 465 μmol). The reaction mixture was maintained at 20 °C for 1.5 h, diluted with ethyl acetate (100 mL), washed with saturated aqueous ammonium chloride (50 mL) followed by saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (40:60 to 50:50 ethyl acetate:hexanes) to provide **159** (208 mg, 84% yield) as a colorless oil: R_F 0.30 (50:50 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.72 (s, 1H), 5.19 (s, 1H), 4.35 (s, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 3.89 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.61 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.49 (app t, *J* = 9.9 Hz, 1H), 2.72-2.53 (comp m, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.17 (dd, *J* = 12.9, 8.7 Hz, 1H), 2.16 (s, 3H), 1.67 (ddd, *J* = 12.9, 6.6, 6.3 Hz, 1H), 1.10 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.3, 155.7, 151.3, 145.7, 144.4, 139.1, 137.1, 133.3, 130.1, 130.0, 128.6, 127.6,

125.0, 122.1, 65.0, 61.1, 61.0, 60.8, 60.4, 56.9, 39.8, 34.3, 32.3, 22.0, 21.8, 18.3, 12.1, 10.3; IR (NaCl/film) 3334, 3200, 2943, 2866, 1687, 1483, 1376, 1176, 1182, 1107, 1007, 995, 664, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{56}N_2O_9S_2Si+H]^+$: *m/z* 801.3275, found 801.3296.



159 161

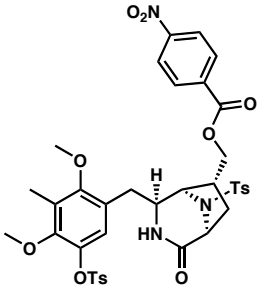
Nitrobenzoate 161

To a solution of **159** (175 mg, 219 μmol) in tetrahydrofuran (4.4 mL) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 328 μL, 328 μmol). After 10 min, the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL) followed by saturated aqueous sodium chloride (35 mL), dried over sodium sulfate, concentrated, and filtered through a pad of silica gel (ethyl acetate eluent) to provide the alcohol (140 mg, 99% yield), which was used without further purification.

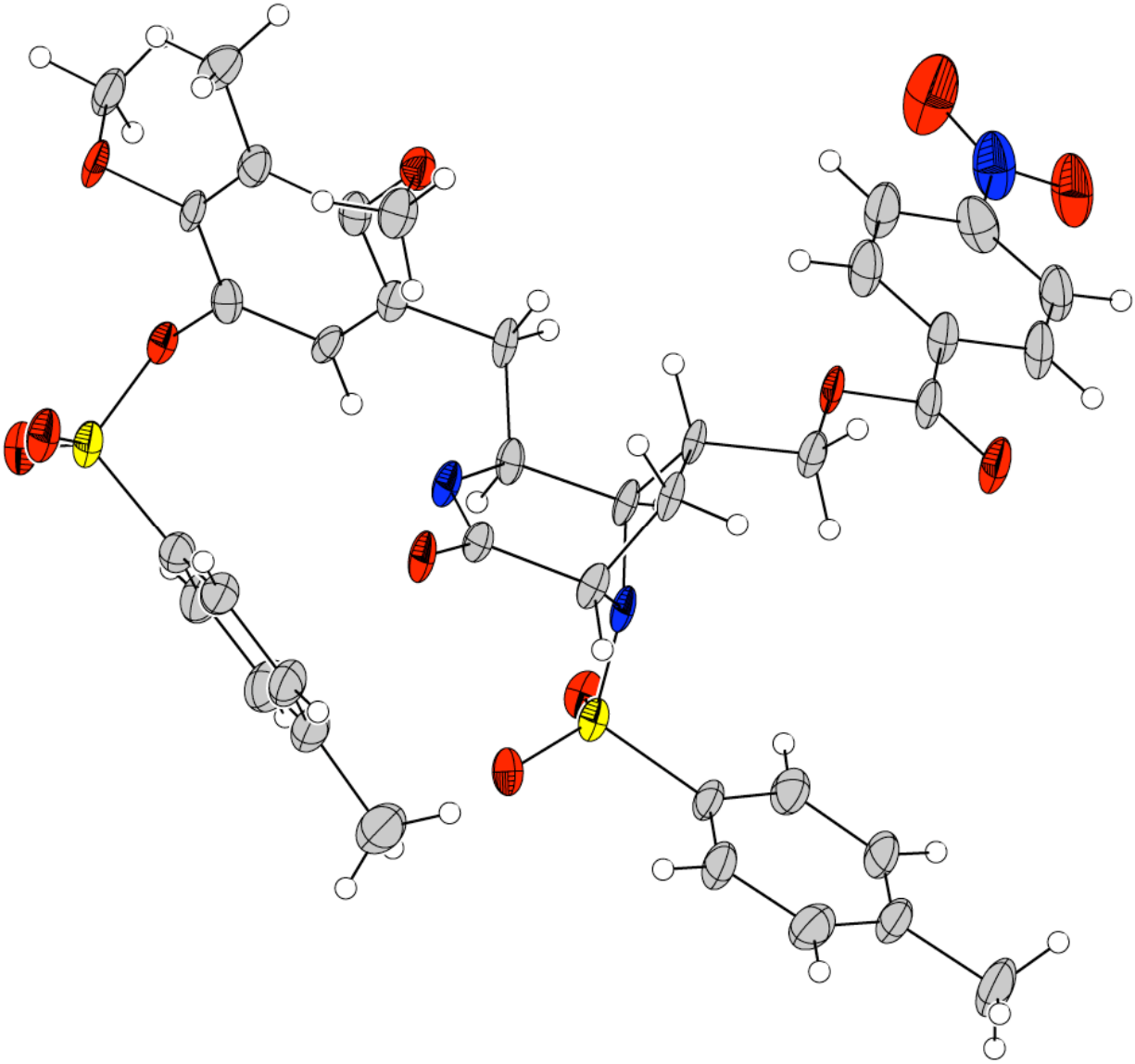
To a solution of the alcohol (60 mg, 93 μmol) in dichloromethane (1.9 mL) were added *N,N*-dimethylaminopyridine (5.7 mg, 46.5 μmol), triethylamine (25.9 μL, 186 μmol), and 4-nitrobenzoyl chloride (25.9 mg, 139.5 μmol). After 10 min the reaction mixture was diluted with dichloromethane (35 mL), washed with water (35 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel

(60:40 ethyl acetate:hexanes eluent) to provide **161** (54.5 mg, 74% yield) as a white, crystalline solid. Crystals of sufficient quality for X-ray analysis were grown from acetone:water by slow evaporation: m.p. 156.5-158 °C (corrected for benzanilide, mp. 163-163.5 °C); R_F 0.47 (85:15 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 9.3 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 1H), 5.22 (s, 1H), 4.43 (dd, *J* = 11.1, 6.6 Hz, 1H), 4.38-4.28 (comp m, 2H), 4.26 (d, *J* = 6.6 Hz, 1H), 3.93 (ddd, *J* = 8.4, 4.4, 4.1 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.00 (ddd, *J* = 14.3, 7.7, 6.9 Hz, 1H), 2.69 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.59 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.37 (dd, *J* = 13.2, 9.0 Hz, 1H), 2.11 (s, 3H), 2.02 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 164.6, 156.1, 151.3, 151.0, 145.8, 144.8, 139.1, 136.6, 135.2, 133.2, 131.0, 130.3, 130.0, 128.6, 127.6, 127.5, 124.1, 124.0, 122.2, 67.1, 61.0, 60.94, 60.91, 60.4, 56.7, 36.0, 35.2, 32.2, 22.0, 21.8, 10.3; IR (NaCl/film) 3338, 3207, 2944, 1726, 1688, 1528, 1349, 1275, 1176, 1161, 1105, 1003, 721 cm^{-1}; HRMS (FAB) calc'd for $[C_{38}H_{39}N_3O_{12}S_2+H]^+$: *m/z* 794.2054, found 794.2047.

Crystal structure of 161



161



Crystal data and structure refinement for 161 (CCDC 219709).

Empirical formula	$C_{38}H_{38}N_3O_{12}S_2 \cdot C_3H_6O$
Formula weight	850.91
Crystallization Solvent	Acetone
Crystal Habit	Blade
Crystal size	0.59 x 0.21 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation	
Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKa	
Data Collection Temperature	100(2) K	
q range for 4790 reflections used in lattice determination	2.31 to 27.48°	
Unit cell dimensions	a = 11.907(2) Å	a= 66.875(2)°
	b = 13.420(2) Å	b= 69.845(3)°
	c = 14.819(3) Å	g = 75.856(3)°
Volume	2028.1(6) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.393 Mg/m^3	

F(000)	894
Data collection program	Bruker SMART v5.054
q range for data collection	1.56 to 28.18°
Completeness to q = 28.18°	88.5 %
Index ranges	$-15 \leq h \leq 15$, $-17 \leq k \leq 17$, $-19 \leq l \leq 18$
Data collection scan type	ω scans at 3 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	17713
Independent reflections	8831 [R_{int}= 0.1081]
Absorption coefficient	0.202 mm^{-1}
Absorption correction	None
Max. and min. transmission (predicted)	0.9860 and 0.8903

Structure solution and Refinement

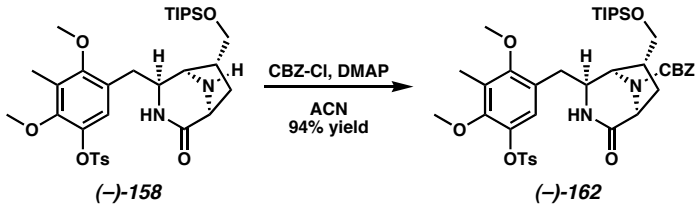
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	8831 / 5 / 517
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.605

Final R indices [I>2s(I), 4683 reflections]	R1 = 0.0784, *w*R2 = 0.1558
R indices (all data)	R1 = 0.1543, *w*R2 = 0.1704
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma 2(Fo2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	1.430 and -0.784 e.Å^{-3}

Special Refinement Details

Refinement of F2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F2, conventional R-factors (R) are based on F, with F set to zero for negative F2. The threshold expression of F2 > 2σ(F2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

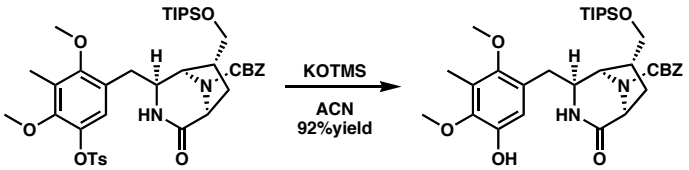
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when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



(–)-158 *(–)-162*

Carbamate (–)-162

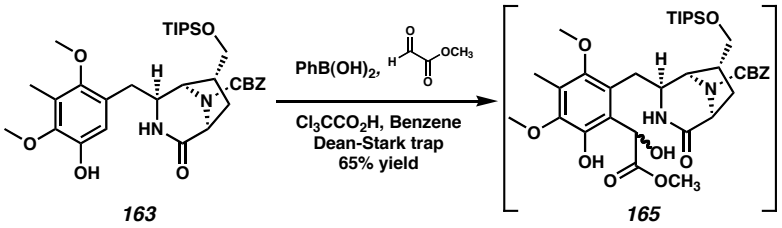
To a solution of **(–)-158** (700 mg, 1.08 mmol) in acetonitrile (21.6 mL) were added *N,N*-dimethylaminopyridine (463 mg, 3.8 mmol) and benzyl-chloroformate (543 μL, 3.8 mmol). After 40 min, the reaction was quenched into saturated aqueous ammonium chloride (150 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:25:50 ethyl acetate:dichloromethane:hexanes eluent) to provide **(–)-162** (794 mg, 94% yield) as a white foam: R_F 0.46 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35-7.23 (comp m, 7H), 6.74 (s, 1H), 5.36 (s, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.33 (s, 1H), 3.93 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.62 (m, 1H), 3.48 (app t, *J* = 9.5 Hz, 1H), 2.70 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.65-2.54 (comp m, 2H), 2.42 (s, 3H), 2.15 (dd, *J* = 12.6, 8.7 Hz, 1H), 2.13 (s, 3H), 1.65 (ddd, *J* = 12.8, 6.6, 6.0 Hz, 1H), 1.05 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 170.9, 156.2, 153.8, 151.2, 145.4, 139.0, 136.3, 133.5, 129.8, 128.6, 128.5, 128.2, 128.0, 127.3, 125.1, 122.1, 67.5, 65.7, 60.9, 60.7, 59.1, 58.8, 56.4, 39.1, 34.0, 32.6, 21.9, 18.3, 12.3, 10.3; IR (NaCl/film) 2943, 2866, 1709, 1685, 1378, 1178, 1109 cm^{-1}; HRMS (FAB) calc'd for $[C_{41}H_{56}N_2O_9SSi+H]^+$: *m/z* 781.3554, found 781.3528; $[\alpha]_D^{25}$ -20.8° (*c* 1.0, acetone).



(–)-162 *(–)-163*

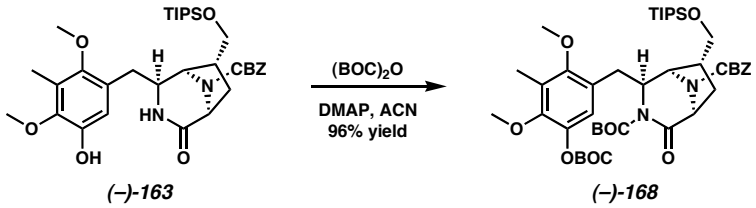
Phenol (–)-163

To a solution of **(–)-162** (1.0 g, 1.28 mmol) in acetonitrile (25 mL) was added potassium trimethylsilanoate (90% grade, 1.82 g, 12.8 mmol). The reaction mixture was maintained at 20 °C for 1.5 h, quenched with saturated aqueous ammonium chloride (25 mL), and stirred vigorously for 10 min. The mixture was diluted with saturated aqueous sodium chloride (150 mL), acidified to pH 5 with concentrated hydrochloric acid, and extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 80:20 ethyl acetate:hexanes eluent) to provide **(–)-163** (735 mg, 92% yield) as a white foam: R_F 0.42 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.37-7.29 (comp m, 5H), 6.59 (s, 1H), 6.03 (s, 1H), 5.66 (s, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 6.6 Hz, 1H), 4.39 (s, 1H), 4.05 (br s, 1H), 3.77 (s, 3H), 3.69-3.61 (comp m, 4H), 3.52 (m, 1H), 2.76 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.71-2.61 (comp m, 2H), 2.23 (s, 3H), 2.20 (dd, *J* = 13.2, 8.7 Hz, 1H), 1.67 (ddd, *J* = 12.8, 6.6, 6.0 Hz, 1H), 1.08 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 171.3, 154.0, 150.5, 145.9, 145.5, 136.4, 128.6, 128.2, 128.0, 125.5, 125.2, 114.2, 67.5, 65.8, 60.8, 59.0, 56.6, 39.3, 34.1, 32.7, 18.3, 12.3, 10.2; IR (NaCl/film) 3306, 2943, 2865, 1709, 1679, 1457, 1418, 1307, 1112 cm^{-1}; HRMS (FAB) calc'd for $[C_{34}H_{50}N_2O_7Si+H]^+$: *m/z* 627.3465, found 627.3469; $[\alpha]_D^{24}$ -30.5° (*c* 1.0, acetone).



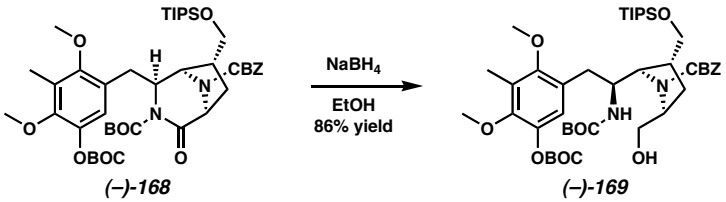
Ester 165

To a solution of phenol **163** (25 mg, 40 μmol) in benzene (2 mL) were added trichloroacetic acid (6.5 mg, 40 μmol), phenylboronic acid (10 mg, 80 μmol), and methyl glyoxylate (25 μL, approximately 280 μmol). The reaction mixture was heated to reflux with removal of water by a Dean-Stark trap for 48 h. After cooling, the mixture was diluted with ethyl acetate (50 mL) and washed with a mixture of saturated aqueous sodium bicarbonate (25 mL) and saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (80:20:0 to 80:20:3 ethyl acetate:hexanes:methanol eluent) to provide ester **165** (18 mg, 65% yield) as a 4:3 mixture of diastereomers: R_F 0.27 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, peaks of the major diastereomer) δ 7.39-7.28 (comp m, 5H), 5.90 (br s, exchangeable, 1H) 5.35 (s, 1H), 5.19 (d, *J* = 12.6 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.52-4.43 (comp m, 2H), 4.03 (s, 1H), 3.98 (app dd, *J* = 5.1, 2.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78-3.60 (comp m, 5H), 2.99-2.61 (comp m, 3H), 2.25 (s, 3H), 2.22-2.14 (m, 1H), 1.68-1.59 (m, 1H), 1.55 (br s, exchangeable, 1H), 1.16-1.01 (comp m, 21H); MS (APCI) calc'd for $[C_{37}H_{54}N_2O_{10}Si+H]^+$: *m/z* 715.4, found 715.4.



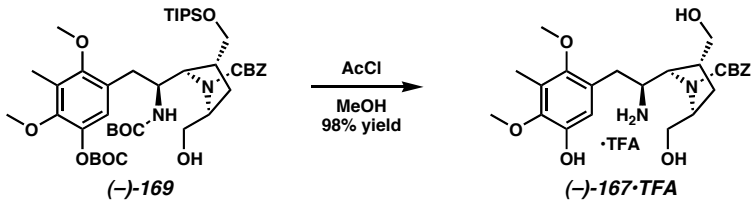
Imide (–)-168

To a solution of **(–)-163** (960 mg, 1.53 mmol) in acetonitrile (15.3 mL) were added *N,N*-dimethylaminopyridine (935 mg, 7.66 mmol) and di-*tert*-butyl dicarbonate (1.67 g, 7.66 mmol). The reaction mixture was maintained at 20 °C for 25 min, diluted with water (150 mL), and extracted with ethyl acetate (2 x 75 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes) to provide **(–)-168** (1.22 g, 96% yield) as an off-white foam: R_F 0.63 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.40-7.22 (comp m, 5H), 6.86 (s, 1H), 5.16 (d, *J* = 12.8 Hz, 1H), 5.04 (d, *J* = 12.8 Hz, 1H), 4.64 (app d, *J* = 6.6 Hz, 2H), 3.93 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.61 (br s, 1H), 3.28 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.10 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.84-2.70 (comp m, 2H), 2.21 (s, 3H), 2.17 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.05 (m, 1H), 1.57 (s, 9H), 1.54 (s, 9H), 0.99 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 169.8, 155.2, 153.4, 152.4, 151.8, 150.1, 140.7, 136.3, 128.6, 128.1, 127.9, 126.2, 124.8, 121.2, 84.1, 83.4, 79.4, 67.4, 65.8, 60.7, 60.1, 57.1, 38.5, 32.9, 30.6, 28.6, 28.2, 28.0, 18.2, 12.2, 10.2; IR (NaCl/film) 2943, 2866, 1762, 1717, 1275, 1234, 1154 cm^{-1}; HRMS (FAB) calc'd for $[C_{44}H_{66}N_2O_{11}Si+H]^+$: *m/z* 827.4515, found 827.4498; $[\alpha]_D^{23}$ -26.2° (*c* 1.0, $CHCl_3$).



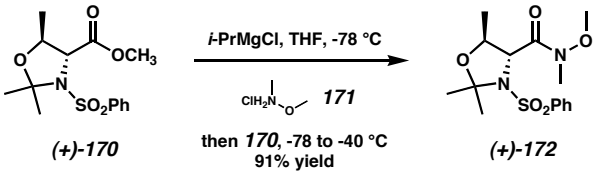
Protected aminotriol (–)-169

To a solution of **(–)-168** (1.22 g, 1.47 mmol) in ethanol (14.7 mL) was added sodium borohydride (1.12 g, 29.5 mmol). The reaction mixture was maintained at 20 °C for 1 h 45 min, then quenched slowly (caution: gas evolution) with saturated aqueous ammonium chloride (100 mL), diluted with water (20 mL), and extracted with dichloromethane (50 mL, 2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:75 to 35:65 ethyl acetate:hexanes eluent) to provide **(–)-169** (1.05 g, 86 % yield) as a white foam: R_F 0.27 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.43-7.29 (comp m, 5H), 6.73 (s, 1H), 5.18 (s, 2H), 4.10 (m, 1H), 3.97-3.85 (comp m, 2H), 3.80 (dd, *J* = 11.6, 2.9 Hz, 1H), 3.75 (s, 3H), 3.63 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.59-3.47 (comp m, 5H), 2.84 (br d, *J* = 11.7 Hz, 1H), 2.46 (br t, *J* = 11.6 Hz, 1H), 2.35 (m, 1H), 2.20 (s, 3H), 2.02-1.86 (comp m, 2H), 1.56 (s, 9H), 1.26 (s, 9H), 1.06 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 157.5, 155.9, 155.2, 151.9, 149.6, 140.4, 136.5, 128.6, 128.3, 128.2, 127.2, 125.5, 121.6, 83.2, 79.2, 67.9, 67.2, 65.8, 65.3, 61.3, 60.7, 60.6, 55.0, 42.4, 33.1, 29.3, 28.5, 28.0, 18.3, 12.3, 10.1; IR (NaCl/film) 3353, 2943, 2866, 1761, 1698, 1275, 1233, 1156 cm^{-1}; HRMS (FAB) calc'd for $[C_{44}H_{70}N_2O_{11}Si+H]^+$: *m/z* 831.4828, found 831.4827; $[\alpha]_D^{24}$ -7.6° (*c* 1.0, acetone).



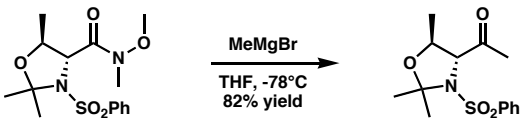
Aminotriol (–)-167

To a cooled (0 °C) solution of **(–)-169** (250 mg, 300 μmol) in methanol (6 mL) was added acetyl chloride (427 μL, 6 mmol) dropwise over 30 seconds. The reaction mixture was warmed to 20 °C for 9 h, concentrated, and purified by preparative HPLC to provide **(–)-167** trifluoroacetate (175 mg, 98% yield) as a colorless, highly viscous oil: R_F 0.11 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, CD_3OD, 50 °C) δ 7.32 (br s, 5H), 6.63 (s, 1H), 5.12 (br s, 2H), 4.11-4.01 (comp m, 2H), 3.99 (app t, *J* = 3.0 Hz, 1H), 3.90 (app td, *J* = 7.4, 2.4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.59-3.46 (comp m, 3H), 2.92 (br s, 1H), 2.75 (m, 1H), 2.50 (ddd, *J* = 13.8, 6.3, 3.7 Hz, 1H), 2.19 (s, 3H), 2.17 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.02 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 75 °C) δ 154.7, 149.2, 145.8, 145.4, 136.3, 128.0, 127.4, 127.0, 124.0, 123.3, 115.2, 66.1, 63.0, 62.1, 60.9, 59.9, 59.1, 58.5, 54.6, 30.3, 28.4, 9.2; IR (NaCl/film) 3272, 2946, 2896, 1694, 1674, 1418, 1204, 1134 cm^{-1}; HRMS (FAB) calc'd for $[C_{25}H_{34}N_2O_7+H]^+$: *m/z* 475.2444, found 475.2445; $[\alpha]_D^{24}$ -11.4° (*c* 0.48, methanol).



Amide (+)-172

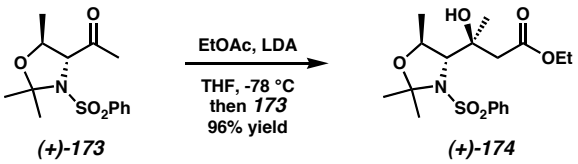
To a –40 °C suspension of *N,O*-dimethylhydroxylamine hydrochloride (**171**) (2.75 g, 28.3 mmol) in tetrahydrofuran (94 mL) was added a solution of isopropylmagnesium chloride in tetrahydrofuran (2 M, 28.2 mL, 56.4 mmol). After 15 min, a solution of ester **(+)-170** (5.90 g, 18.8 mmol) in tetrahydrofuran (37.7 mL) was added. The mixture was maintained at –40 °C for 3.5 h and then quenched with saturated aqueous ammonium chloride (200 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (80:20 to 60:40 hexanes:ethyl acetate eluent) to provide amide **(+)-172** (5.88 g, 91% yield) as a white solid: R_F 0.27 (50:50 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.01 (comp m, 2H), 7.63-7.51 (m, 3H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.26 (m, 1H), 3.80 (s, 3H), 3.23 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 128.8, 128.0, 97.3, 74.8, 64.2, 61.4, 27.4, 18.8; IR (NaCl/film) 2982, 1677, 1447, 1344 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{15}H_{22}N_2O_5S+H]^+$: 343.1328, found 343.1312; $[\alpha]_D^{25}$ +71.9° (*c* 1.0, $CHCl_3$).



(+)-172 *(+)-173*

Ketone (+)-173

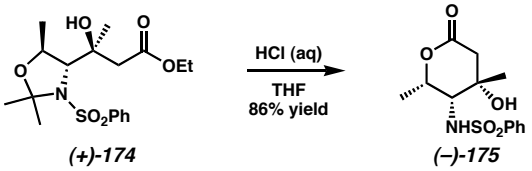
To a –78 °C solution of amide **(+)-172** (1.64 g, 4.79 mmol) in tetrahydrofuran (20 mL) was added methylmagnesium bromide (1.8 mL, 5.4 mmol). After 45 min, additional methylmagnesium bromide (1.8 mL, 5.4 mmol) was added. The solution was allowed to warm to 22 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (4:1 to 1:1 hexanes:ethyl acetate eluent) to yield ketone **(+)-173** (1.30 g, 82% yield) as a white solid: R_F 0.38 (70:30 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.64-7.51 (comp m, 3H), 4.22 (m, 1H), 3.70 (d, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 1.69 (s, 3H), 1.49 (s, 3H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 139.7, 133.1, 129.2, 127.8, 98.2, 74.6, 72.8, 28.8, 25.8, 25.0, 17.9; IR (NaCl/film) 2987, 1716, 1344, 1157 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{14}H_{19}NO_4S+H]^+$: 298.1113, found 298.1101; $[\alpha]_D^{26}$ +148.0° (*c* 1.0, $CHCl_3$).



Ester (+)-174

To a 0 °C solution of diisopropylamine (11.3 mL, 80.9 mmol) in tetrahydrofuran (77 mL) was added *n*-butyllithium (30 mL, 76 mmol). After 20 min, the solution was cooled to -78 °C, and a solution of ethyl acetate (7.5 mL, 77 mmol) in tetrahydrofuran (154 mL) was added dropwise over 5 min. After 1 h, a solution of ketone **(+)-173** (4.83 g, 16.2 mmol) in tetrahydrofuran (81 mL) at -78 °C was added via cannula. After 2.5 h the reaction mixture was quenched with saturated aqueous ammonium chloride (100 mL). The mixture was allowed to warm to 22 °C and partitioned between water (100 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organics were dried over magnesium sulfate. Solvent was evaporated and the residue was purified by flash chromatography on silica gel (10:10:80 to 15:15:70 ethyl acetate:dichloromethane:hexanes eluent) to provide aldol adduct **(+)-174** (6.01 g, 96% yield) as a colorless oil: R_F 0.61 (50:25:25 hexanes:dichloromethane:ethyl acetate eluent); ^{1}H NMR (300 MHz, C_6D_6) δ 7.92-7.89 (comp m, 2H), 6.93-6.90 (m, 3H), 4.52 (dq, *J* = 6.6, 2.0 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 4.08-3.90 (comp m, 2H), 3.30 (d, *J* = 17.0 Hz, 1H), 2.47 (d, *J* = 17.0 Hz, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 140.6, 133.2, 129.1, 128.6, 99.8, 74.9, 72.8, 72.0, 61.0, 42.9, 31.2, 28.8, 24.4, 22.5, 14.4; IR

(NaCl/film) 3480, 2986, 1710, 1447, 1346, 1204 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{18}H_{27}NO_6S+H]^+$: 386.1637, found 386.1637; $[\alpha]_D^{26}$ +64.0° (*c* 2.0, acetone).

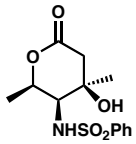


(+)-174 *(–)-175*

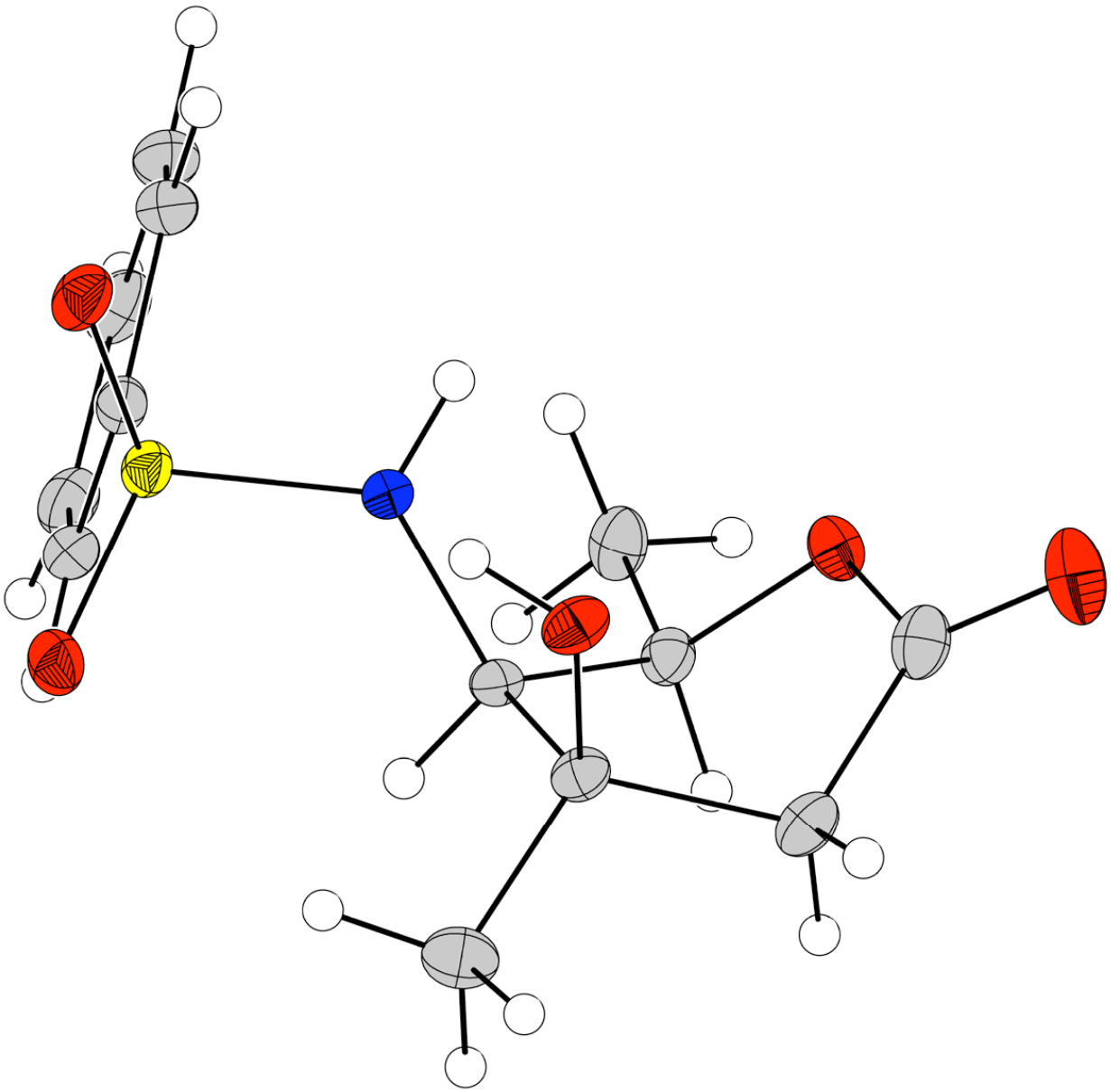
Lactone (–)-175

To a solution of ester **(+)-174** (0.467g, 1.21 mmol) in tetrahydrofuran (12 mL) was added aqueous hydrochloric acid (1 M, 0.242 mL, 0.242 mmol). After 13 h, the reaction was quenched with saturated aqueous sodium bicarbonate (50 mL), extracted with ethyl acetate (2 x 30 mL), and dried over sodium sulfate. Solvent was evaporated and the residue was purified by flash chromatography on silica gel (25:25:50 to 30:30:40 acetone:dichloromethane:hexanes eluent) to afford lactone **(–)-175** (0.312 g, 86% yield) as a white solid. Crystals of sufficient quality for X-ray analysis of lactone **(+)-175** (prepared analogously from L-threonine) were grown from dichloromethane by slow evaporation: uncorrected mp. 164-165 °C; R_F 0.20 (50:25:25 hexanes:dichloromethane: acetone eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.01-7.90 (comp m, 2H), 7.68-7.56 (comp m, 3H), 4.61 (dq, *J* = 6.6 , 4.5 Hz, 1H), 3.66 (d, *J* = 4.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.50 (d, *J* = 16.0 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 140.7, 133.2, 129.4, 127.3, 76.0, 69.9, 59.3, 43.2, 27.5, 16.6; IR (NaCl/film) 3496, 3289, 2996, 1738, 1448, 1337 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{13}H_{17}NO_5S+H]^+$: 300.0906, found 300.0909; $[\alpha]_D^{26}$ -74.2° (*c* 1.0, $CHCl_3$).

Crystal Structure of (+)-175



(+)-175



Crystal data and structure refinement for (+)-175 (CCDC 217756).

Empirical formula	$C_{13}H_{17}NO_5S$
Formula weight	299.34
Crystal Habit	Prism
Crystal size	0.35 x 0.31 x 0.26 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKa
Data Collection Temperature	100(2) K
q range for 21790 reflections used	
in lattice determination	2.77 to 28.06°
Unit cell dimensions	a = 8.0871(4) Å
	b = 8.2042(4) Å
	c = 20.6350(10) Å
Volume	1369.09(12) $Å^3$
Z	4
Crystal system	Orthorhombic
Space group	P212121
Density (calculated)	1.452 Mg/m^3
F(000)	632
Data collection program	Bruker SMART v5.054

q range for data collection	1.97 to 28.28°
Completeness to q = 28.28°	96.1 %
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-26 \leq l \leq 26$
Data collection scan type	ω scans at 7 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	27404
Independent reflections	3217 [R_{int}= 0.0507]
Absorption coefficient	0.255 mm^{-1}
Absorption correction	None
Max. and min. transmission (predicted)	0.9366 and 0.9159

Structure solution and Refinement

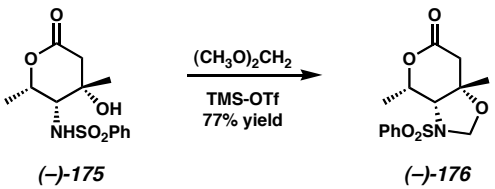
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3217 / 0 / 249
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	2.819
Final R indices [$I>2\sigma(I)$, 3121 reflections]	R1 = 0.0288, *w*R2 = 0.0590
R indices (all data)	R1 = 0.0298, *w*R2 = 0.0591

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
Absolute structure parameter	0.02(5)
Largest diff. peak and hole	0.449 and -0.350 e.$Å^{-3}$

Special Refinement Details

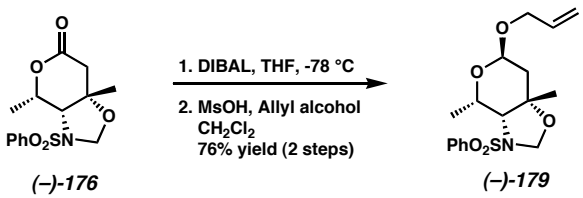
Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not 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.



Oxazolidine (–)-176

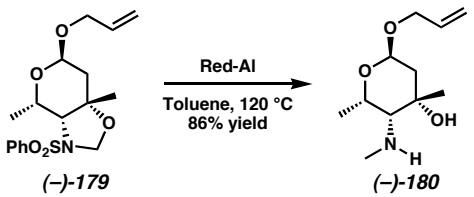
To a suspension of lactone **(–)-175** (2.92 g, 9.75 mmol) in dimethoxymethane (49 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (5.3 mL, 29 mmol) dropwise over 3 min. After 20 min, the reaction was quenched with saturated aqueous sodium bicarbonate (100 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (75 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (15:15:70 to 30:30:40 acetone:dichloromethane:hexanes eluent) to provide oxazolidine **(–)-176** (2.34 g, 77% yield) as a white solid: R_F 0.46 (50:25:25 hexanes: dichloromethane:acetone eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (comp m, 2H), 7.75-7.58 (comp m, 3H), 5.23 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 4.49 (dq, *J* = 6.3 , 2.7 Hz, 1H), 3.80 (d, *J* = 2.7 Hz, 1H), 2.74 (d, *J* = 16.0 Hz, 1H), 2.54 (d, *J* = 16.0 Hz, 1H), 1.61 (d, *J* = 6.3 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 137.8, 134.1, 129.8, 128.3, 82.0, 81.7, 75.0, 65.2, 40.9, 25.6, 17.3; IR (NaCl/film) 3430, 2902, 1765, 1446 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{14}H_{17}NO_5S+H]^+$: 312.0906, found 312.0909; $[\alpha]_D^{25}$ -151.0° (*c* 1.0, $CHCl_3$).



Bicycle (–)-179

To a –78 °C solution of oxazolidine **(–)-176** (1.94 g, 6.23 mmol) in tetrahydrofuran (62 mL) was added diisobutylaluminum hydride (2.2 mL, 12 mmol) dropwise over 1 min. After 30 min, the reaction was quenched with aqueous sodium potassium tartrate (1 M, 100 mL). Organics were extracted with ethyl acetate (2 x 50 mL), dried over magnesium sulfate, and concentrated. The residue was further dried by azeotropic removal of water with benzene. The crude residue was dissolved in dichloromethane (62 mL), and allyl alcohol (6.35 mL, 93.4 mmol) and methanesulfonic acid (0.81 mL, 1.2 mmol) were added. After 18 h, the reaction was quenched with saturated aqueous sodium bicarbonate (100 mL). The mixture was extracted with dichloromethane (50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10:90 to 15:85 ethyl acetate:hexanes eluent) to afford bicycle **(–)-179** (1.67 g, 76% yield) as a colorless oil: R_F 0.17 (85:15 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.87 (comp m, 2H), 7.65-7.51 (comp m, 3H), 5.87 (m, 1H), 5.25 (appt. ddd, *J* = 17.1, 3.3, 1.8 Hz, 1H), 5.29-5.12 (comp m, 2H), 4.84 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.81 (d, *J* = 5.7 Hz, 1H), 4.20 (ddt, *J* = 13.2, 5.7, 1.8 Hz, 1H), 4.04 (dq, *J* = 6.6, 2.7 Hz, 1H), 3.96 (ddt, *J* = 11.7, 5.1, 1.2 Hz, 1H), 3.53 (d, *J* = 2.4 Hz, 1H), 2.17 (dd, *J* = 15.6, 6.3 Hz, 1H), 1.64 (dd, *J* = 15.3, 8.4 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 138.7, 134.8, 133.6, 129.5, 128.1, 117.1, 95.9, 81.4, 81.0, 68.4, 65.7, 65.6, 37.8, 26.3, 17.4; IR (NaCl/film) 2981, 1447, 1353, 1166 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{17}H_{23}NO_5S+H]^+$: 354.1375, found 354.1373; $[\alpha]_D^{26}$ -140.5° (*c* 1.00, $CHCl_3$).

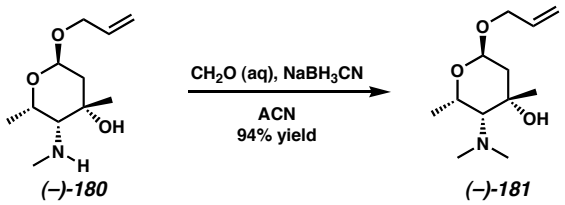


(–)-179 *(–)-180*

Glycoside (–)-180

To a solution of bicycle **(–)-179** (0.554 g, 1.57 mmol) in toluene (16 mL) was added Red-Al (65% w/w in toluene, 3.53 mL, 11.7 mmol). The mixture was heated to reflux for 2 h 45 min and cooled to 0 °C. Celite (1.0 g) and saturated aqueous sodium sulfate (1.0 mL) were added, in that order. The mixture was allowed to warm to 22 °C and filtered. The solids were washed with ethyl acetate (50 mL) and saturated aqueous sodium chloride (15 mL). The combined filtrates were phase-separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (90:10:0.1:0.5 to 90:10:2:0.5 chloroform:ethyl acetate:methanol:triethylamine eluent) to provide glycoside **(–)-180** (0.290 g, 86% yield) as a colorless oil: R_F 0.09 (95:5 dichloromethane:methanol eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.24 (appt. ddd, *J* = 17.7, 3.3, 1.5 Hz, 1H), 5.15 (appt. ddd, *J* = 10.5, 3.3, 1.8 Hz, 1H), 4.79 (d, *J* = 4.2 Hz, 1H), 4.16 (dq, *J* = 5.7, 0.9 Hz, 1H), 4.10 (ddt, *J* = 13.2, 4.8, 1.8 Hz, 1H), 3.89 (ddt, *J* = 13.2, 6.0, 1.5 Hz, 1H), 2.59 (s, 3H), 2.02 (s, 1H), 1.72 (appt. d, *J* = 14.1 Hz, 1H),

1.59 (dd, *J* = 13.8, 4.5 Hz, 1H), 1.41 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 116.6, 90.0, 68.2, 68.0, 67.7, 64.9, 40.0, 38.7, 26.1, 18.5; IR (NaCl/flim) 3345, 2932, 1118 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{11}H_{20}NO_3+H]^+$: 216.1600, found 216.1603; $[\alpha]_D^{26}$ -185.3° (*c* 1.00, $CHCl_3$).

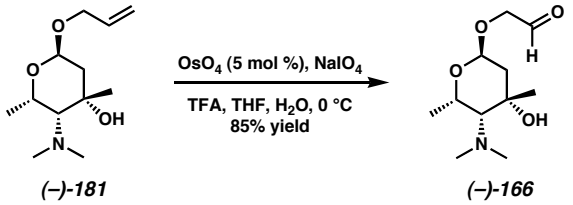


(–)-180 *(–)-181*

***N,N*-Dimethyl pyranose (–)-181**

To a solution of amine **(–)-180** (0.430 g, 2.00 mmol) in acetonitrile (20 mL) was added sodium cyanoborohydride (0.377 g, 6.00 mmol). After 5 min, aqueous formaldehyde (37% w/w in water, 0.75 mL, 10 mmol) was added. The mixture was stirred vigorously for 2 h, and the reaction was quenched with glacial acetic acid (0.86 mL). After concentrating to 5 mL volume, the solution was diluted with aqueous sodium hydroxide (1 M, 15 mL) and saturated aqueous sodium chloride (40 mL). The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (90:10:0.1:0.5 to 90:10:1.5:0.5 chloroform:ethyl acetate:methanol:triethylamine eluent) to yield dimethylamino pyranose **(–)-181** (0.429 g, 94% yield) as a colorless oil: R_F 0.45 (90:10 chloroform:methanol eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.35-5.10 (comp m, 2H), 5.14 (appt. dd, *J* = 10.5, 1.8 Hz, 1H), 4.93 (t, *J* = 2.7 Hz, 1H), 4.25 (dq, *J* = 7.2, 2.7 Hz, 1H), 4.09 (ddt, *J* = 13.2, 5.1, 0.9 Hz, 1H), 3.91 (ddt, *J* = 13.2,

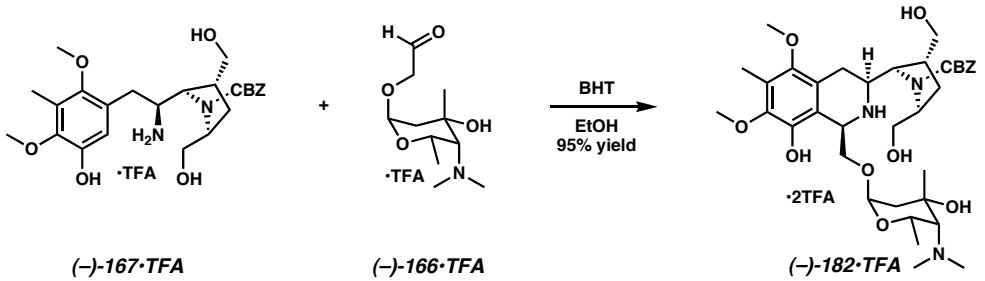
5.7, 1.5 Hz, 1H), 2.68 (s, 3H), 2.21 (d, *J* = 2.7 Hz, 1H), 1.88 (d, *J* = 2.7 Hz, 2H), 1.43 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 116.3, 97.0, 69.4, 67.9, 66.2, 62.2, 45.0, 41.0, 29.5, 19.0; IR (NaCl/film) 3288, 2937, 1395, 1119 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{12}H_{22}NO_3 + H]^+$: 230.1756, found 230.1754; $[\alpha]_D^{24}$ -158.5° (*c* 1.0, acetone).



Glycosyloxyacetaldehyde (–)-166

To a 0 °C solution of glycoside **(–)-181** (0.060 g, 0.26 mmol) in tetrahydrofuran (4.8 mL) and water (0.48 mL) were added trifluoroacetic acid (0.10 mL, 1.3 mmol), osmium tetroxide (3.3 mg, 0.013 mmol), and sodium periodate (0.14 g, 0.65 mmol). The reaction mixture was maintained at 0 °C for 16 h and then quenched with aqueous potassium hydroxide (10 M, 0.13 mL). After diluting with ethanol (5 mL), the mixture was filtered through a pad of silica gel, concentrated, and purified by preparative thin layer chromatography (15:85 methanol:chloroform eluent) to afford aldehyde **(–)-166** as its trifluoroacetate salt (50.1 mg, 55% yield) and aldehyde **(–)-166** as the free base (18.4 mg, 30% yield): R_F 0.25 (10:90 methanol:chloroform eluent); ^{1}H NMR (300 MHz, CD_3OD) δ 4.90 (d, *J* = 4.5 Hz, 1H), 4.62 (appt. dt *J* = 8.4, 5.7 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 3.47 (m, 1H), 3.38 (m, 1H), 2.68 (s, 6H), 2.30 (s, 1H), 1.88 (dd, *J* = 13.8, 4.5 Hz, 1H), 1.78 (d, *J* = 14.4 Hz, 1H), 1.39 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75

MHz, CD_3OD) δ 97.8, 96.7, 69.7, 69.6, 69.2, 67.2, 65.5, 43.9, 40.4, 28.7, 18.0; IR (NaCl/film) 3290, 2937, 2836, 1682, 1127 cm^{-1}; $[\alpha]_D^{25}$ -122.5° (*c* 0.45, CH_2Cl_2).

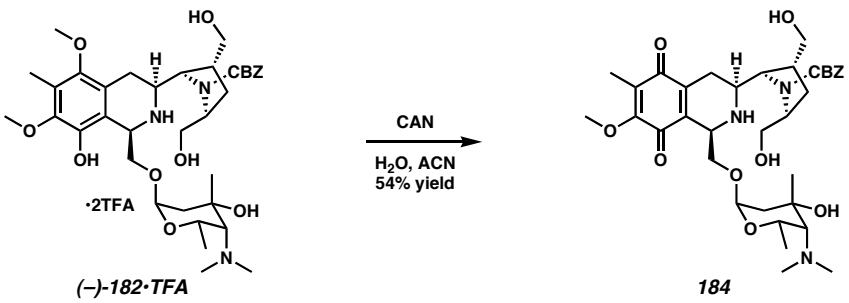


(–)-167·TFA *(–)-166·TFA* *(–)-182·TFA*

Tetrahydroisoquinoline (–)-182

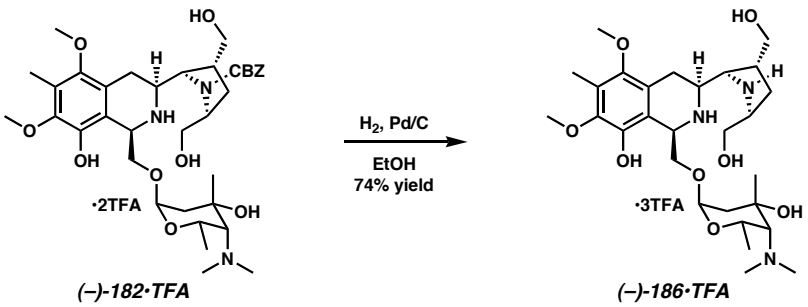
To neat **(–)-167** trifluoroacetate (50 mg, 85 μmol) were added 2,6-di-*tert*-butyl-4-methyl phenol (9.3 mg, 42.5 μmol) and a solution of **(–)-166** trifluoroacetate (50 mg, 144.7 μmol) in ethanol (1.7 mL). The reaction mixture was sealed under argon in a foil-wrapped vial at 20 °C. After 36 h, additional **(–)-166** (5 mg, 21.6 μmol) was added. After 63 h, the reaction mixture was concentrated and purified by preparative HPLC to provide **(–)-182** bis-trifluoroacetate (74 mg, 95% yield) as a colorless, highly viscous oil: R_F 0.27 (10:90 methanol:chloroform); ^1H NMR (300 MHz, CD_3OD, 45 °C) δ 7.43-7.32 (comp m, 5H), 5.29 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 3.3 Hz, 1H), 4.97 (s, 1H), 4.51 (br d, *J* = 7.8 Hz, 1H), 4.18 (m, 1H), 4.02 (br d, *J* = 8.7 Hz, 1H), 3.83 (app d, *J* = 9.9 Hz, 1H), 3.80-3.57 (comp m, 6H), 3.73 (s, 3H), 3.64 (s, 3H), 3.36 (d, *J* = 6.6 Hz, 1H), 3.04 (s, 6H), 3.01 (s, 1H), 2.62-2.46 (comp m, 2H), 2.21 (s, 3H), 2.13-2.01 (comp m, 3H), 1.93 (ddd, *J* = 21.9, 11.3, 10.8 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD, 50 °C) δ 159.5, 150.1, 146.8, 144.4, 137.4, 129.7, 129.4, 128.9, 126.0, 124.0, 115.5, 98.1, 72.1, 69.5, 67.9, 66.8, 64.9, 64.5, 63.9,

63.5, 61.7, 61.3, 61.2, 57.5, 55.4, 44.8, 39.9, 30.8, 30.5, 21.9, 18.6, 10.0; IR (NaCl/film) 3307, 3064, 2945, 1682, 1204, 1180, 1131 cm^{-1}; HRMS (FAB) calc'd for $[C_{36}H_{53}N_3O_{10}+H]^+$: *m/z* 688.3809, found 688.3835; $[\alpha]_D^{26}$ -71.3° (*c* 0.5, methanol).



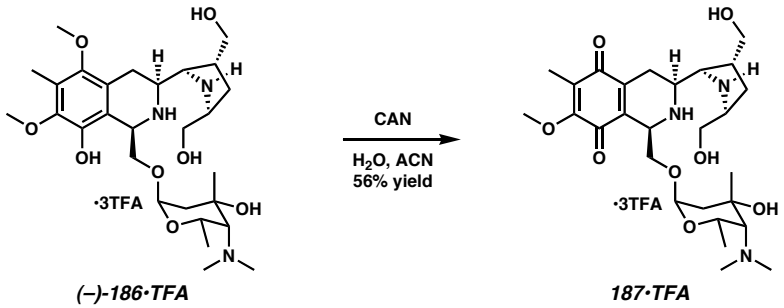
Quinone 184

To a 0 °C solution of **(–)-182** bis-trifluoroacetate (10 mg, 10.9 μmol) in acetonitrile (953 μL) was added a solution of ammonium cerium(IV) nitrate (14.9 mg, 27.2 μmol) in water (136 μL). After 10 min, the reaction was quenched into a mixture of saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous sodium chloride (10 mL) and extracted into ethyl acetate (3 x 15 mL). The organics were dried over sodium sulfate, concentrated, and purified by preparative thin-layer chromatography on silica gel (15:85 methanol:chloroform eluent) to provide **184**: R_F 0.35 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (comp m, 5H), 5.19 (d, *J* = 12.6 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 4.86 (br s, 1H), 4.29 (app d, *J* = 7.5 Hz, 1H), 4.18-4.10 (m, 1H), 3.99 (s, 3H), 3.84 (dd, *J* = 7.2, 2.7 Hz, 1H), 3.75-3.67 (m, 1H), 3.65-3.47 (comp m, 5H), 2.69 (d, *J* = 2.5 Hz, 1H), 2.64 (s, 6H), 2.45-2.36 (m, 1H), 2.08 (d, *J* = 2.7 Hz, 1H), 1.95 (s, 3H), 1.92-1.77 (comp m, 3H), 1.42-1.34 (comp m, 2H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.15 (s, 3H).



Tetrahydroisoquinoline (–)-186

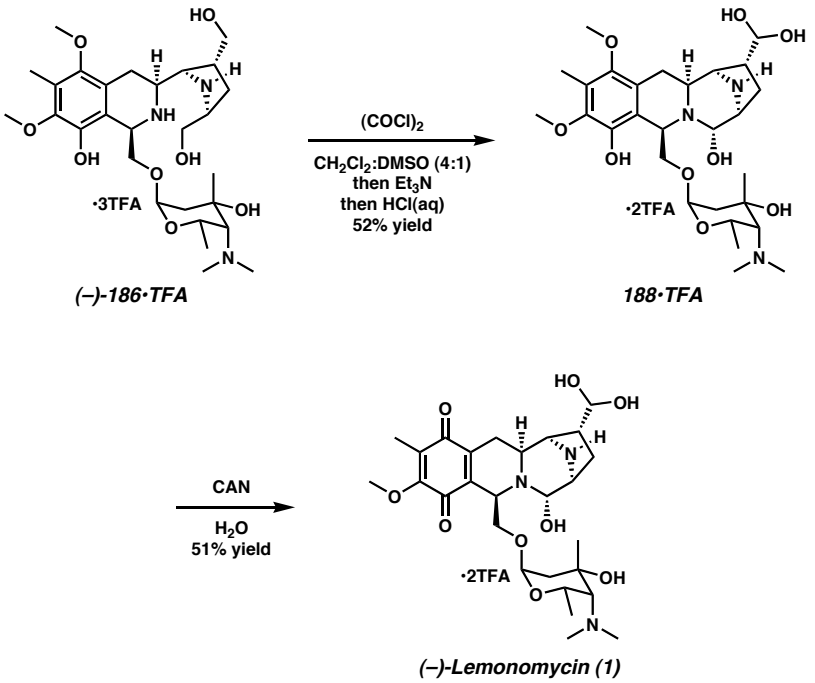
To a solution of **(–)-182** bis-trifluoroacetate (74 mg, 80.7 μmol) in ethanol (8 mL) was added palladium on carbon (10% w/w, 15 mg). The reaction mixture was purged and flushed with hydrogen, then maintained under a balloon of hydrogen for 30 min. The mixture was filtered through celite, concentrated, and purified by preparative HPLC to provide **(–)-186** tris-trifluoroacetate (53.5 mg, 74% yield) as a colorless, highly viscous oil: R_F 0.25 (10:90 methanol: chloroform, eluted twice); ^{1}H NMR (300 MHz, D_2O) δ 5.17 (s, 1H), 5.11 (d, *J* = 3.9 Hz, 1H), 4.66 (dd, *J* = 10.8, 3.3 Hz, 1H), 4.01-3.85 (comp m, 4H), 3.82-3.61 (comp m, 5H), 3.77 (s, 3H), 3.71 (s, 3H), 3.34 (dd, *J* = 16.8, 2.4 Hz, 1H), 3.04 (s, 6H), 3.00 (s, 1H), 2.89 (dd, *J* = 16.5, 12.6 Hz, 1H), 2.75 (m, 1H), 2.24 (s, 3H), 2.22-1.93 (comp m, 3H), 1.89 (d, *J* = 15.0 Hz, 1H), 1.52 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 148.2, 145.0, 142.9, 125.6, 122.3, 114.1, 96.2, 70.2, 67.2, 64.2, 64.0, 62.5, 62.1, 61.1, 61.0, 60.9, 60.1, 55.6, 54.2, 47.2, 43.5, 41.9, 37.3, 28.5, 27.9, 24.8, 17.5, 9.1; IR (NaCl/film) 3296, 2947, 1682, 1468, 1417, 1204, 1131, 1054, 1004, 800, 723 cm^{-1}; HRMS (FAB) calc'd for $[C_{28}H_{47}N_3O_8+H]^+$: *m/z* 554.3441, found 554.3463; $[\alpha]_D^{24}$ -83.1° (*c* 0.25, methanol).



(–)-186·TFA *187·TFA*

Quinone 187

To a 0 °C solution of **(–)-186** tris-trifluoroacetate (6.3 mg, 7.0 μmol) in acetonitrile (525 μL) and water (100 μL) was added a solution of ammonium cerium(IV) nitrate (9.6 mg, 17.5 μmol) in water (75 μL). After 15 min, the reaction mixture was diluted with water (3 mL) and purified by preparative HPLC to provide **187** tris-trifluoroacetate: R_F 0.25 (10:90 methanol:chloroform, eluted twice); ^{1}H NMR (600 MHz, D_2O) δ 5.15 (d, *J* = 6.0 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.01 (app q, *J* = 10.8 Hz, 1H), 3.91 (s, 3H), 3.96-3.89 (m, 1H), 3.87-3.81 (comp m, 2H), 3.80-3.73 (comp m, 2H), 3.61 (dd, *J* = 12.0, 10.8 Hz, 1H), 3.52-3.45 (m, 1H), 3.23-3.17 (comp m, 2H), 3.10-3.04 (comp m, 7H), 2.70-2.63 (m, 1H), 2.57 (app ddd, *J* = 18.0, 12.0, 3.6 Hz, 1H), 2.15-1.93 (comp m, 5H), 1.98 (s, 3H), 1.56 (d, *J* = 10.8 Hz, 1.37 (s, 3H); MS (APCI) calc'd for $[C_{27}H_{44}N_3O_8]^+$: *m/z* 538.4, found 538.7.



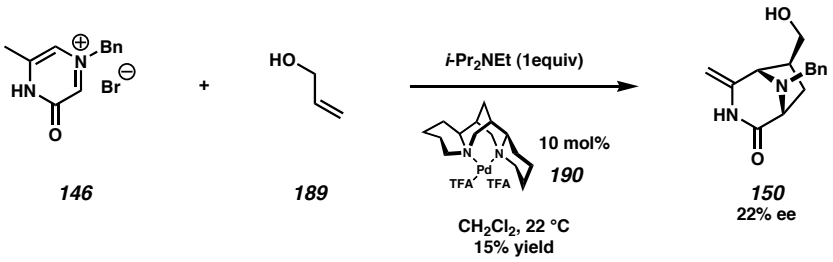
(–)-186·TFA *188·TFA* *(–)-Lemonomycin (1)*

188 and (–)-Lemonomycin (1)

To a -78 °C solution of dimethyl sulfoxide (7.9 μL, 111.6 μmol) in dichloromethane (744 μL) was added oxalyl chloride (4.9 μL, 55.8 μmol). After 30 min, this solution was added via cannula to a -78 °C solution of **(–)-186** tris-trifluoroacetate (10.0 mg, 11.16 μmol) in 4:1 dichloromethane:dimethyl sulfoxide (560 μL). The reaction mixture was maintained at -78 °C for 1h, after which triethylamine (23.3 μL, 167.4 μmol) was added. After an additional 15 min, the reaction mixture was warmed to 0 °C over 10 min. The reaction mixture was extracted into 1M aqueous hydrochloric acid (2 x 1 ml) and warmed to 20 °C for 41 h. The mixture was then purified by preparative HPLC to provide **188** bis-trifluoroacetate (4.6 mg, 52% yield) as a colorless film, which was used immediately in the next reaction.

To a cooled (0 °C) solution of **188** bis-trifluoroacetate (4.6 mg, 5.78 μmol) in water (1.16 mL) was added cerium(IV) ammonium nitrate (7.9 mg, 14.5 μmol). After 10

min, the reaction mixture was purified by preparative HPLC to provide (–)-lemonomycin (**1**, 2.3 mg, 51% yield) as a bright yellow film: ^{1}H NMR (600 MHz, D_2O) δ 5.16 (d, *J* = 4.8 Hz, 1H), 5.08 (d, *J* = 4.8 Hz, 1H), 4.90 (d, *J* = 3.6 Hz, 1H), 4.29 (s, 1H), 4.08 (dd, *J* = 6.6, 2.4 Hz, 1H), 4.01 (s, 1H), 3.98 (br q, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.77 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.66 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.37 (br d, *J* = 9.6 Hz, 1H), 3.16 (s, 1H), 3.054 (s, 3H), 3.048 (s, 3H), 2.77 (dd, *J* = 17.4, 2.4 Hz, 1H), 2.64 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H), 2.17-1.98 (comp m, 4H), 1.97 (s, 3H), 1.92 (d, *J* = 14.4 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 190.3, 184.6, 158.2, 144.6, 140.6, 133.4, 99.8, 92.9, 81.3, 72.6, 71.3, 69.7, 64.9, 64.1, 63.3, 62.8, 54.4, 52.4, 49.7, 44.4, 43.4, 40.6, 31.3, 28.5, 26.5, 19.9, 11.0; IR (NaCl/film) 3249, 3094, 2943, 1673, 1611, 1443, 1387, 1329, 1207, 1137, 802, 724 cm^{-1}; UV-Vis (methanol) λ_{max} 272, 363 nm; HRMS (FAB) calc'd for $[C_{27}H_{41}N_3O_9\text{-}OH]^+$: *m/z* 534.2815, found 534.2839; $[\alpha]_D^{23}$ -124.2° (*c* 0.1, H_2O).



Alcohol 150 by Catalytic Asymmetric Dipolar Cycloaddition

To a suspension of **146** (20 mg, 71.1 μmol) in dichloromethane (711 μL) was added diisopropylethylamine (12.4 μL, 71.1 μmol), affording a clear solution. After 10 min, palladium complex **190** (4.0 mg, 7.1 μmol) and allyl alcohol (14.5 μL, 213.3 μmol)

were added. After 96 h, the reaction mixture was purified by preparative thin-layer chromatography on silica gel to yield alcohol **150** (2.7 mg, 15% yield) as a colorless oil. The spectral data of this compound matched with samples generated by non-catalyzed cycloadditions. HPLC analysis (Chiracel AD column, 10:90 2-propanol:hexanes, 1 mL/min, λ = 254 nm) showed the product to be of 22% ee (t_{fast} = 17.95 min, minor; t_{slow} = 22.28 min, major).

2.8 Notes and Citations

(1) 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.

(2) Our total synthesis of (–)-lemonomycin has been communicated, see: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000-15001.

(3) (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.

(4) Pictet-Spengler cyclizations have been utilized for the synthesis of several tetrahydroisoquinoline antitumor antibiotics. For a comprehensive review of the chemistry and biology of these compounds, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

(5) This synthetic route is precedented by a similar series of reactions leading to L-callipeltose, see: Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133-3136.

(6) For recent examples of catalytic asymmetric hetero-Diels-Alder reactions, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b)

Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Nat'l. Acad. Sci.* **2004**, *101*, 5846-5850. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398-2400. (d) Schaus, S. E.; Brnalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403-405.

(7) The formylation and Baeyer-Villiger oxidation follow known procedures, see: (a) Kaliakoudas, D.; Eugster, C. H.; Ruedi, P. *Helv. Chim. Acta* **1990**, *73*, 48-62. (b) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Åkermark, B.; Bäckvall, J.-E. *J. Org. Chem.* **1984**, *49*, 4740-4741.

(8) The selective substitution of 2,6-dichloropyrazine with sodium benzyloxide is known, see: Cheeseman, G. W. H.; Törzs, E. S. G. *J. Chem. Soc.* **1965**, 6681-6688.

(9) The zinc was preactivated with ethereal hydrogen chloride, and excess zinc was removed by filtration prior to the palladium catalyzed coupling step.

(10) For Negishi coupling of benzylic zinc reagents with chloropyridines, see: (a) Shiota, T.; Yamamor, T. *J. Org. Chem.* **1999**, *64*, 453-457. (b) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 845-848. For a general review of the Negishi reaction, see: (c) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. Palladium- or Nickel-catalyzed Cross-coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling.

Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; Wiley-VHC: Weinheim, 2004; 2, 815-889.

(11) For examples of multimeric organozinc enolate complexes, see: (a) van der Steen, F. H.; Boersma, J.; Spek, A. L.; Van Koten, G. *Organometallics* **1991**, *10*, 2467-2480. (b) Dekker, J.; Budzelaar, P. H. M. Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403-1407.

(12) Since an excess of insoluble zinc metal is present throughout the reaction, the unusual product distribution may be the result of complex surface chemistry.

(13) The reaction protocol for this dipolar cycloaddition is based on the pioneering work of Joule, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett*. **1987**, *28*, 2187-2190. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett*. **1990**, *31*, 4781-4782. (c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331-347.

(14) Williams has developed an oxidative dipolar cycloaddition for the synthesis of related natural products, see: Scott, J. D.; Williams, R. M. *J. Am. Chem. Soc*. **2002**, *124*, 2951-2956 and references therein.

(15) Due to their instability, oxidopyrazinium **139** was characterized only by ^{1}H NMR, and no attempt was made to characterize dipole **140**. Due to the inseparability of

the various cycloadducts **141**, none were fully characterized before advancement to silyl ether **142**.

(16) Oxidopyrazinium **146** was reported by Joule as a substrate for dipolar cycloaddition with a variety of electron poor olefins, although not with acrolein, see reference 13.

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

(18) Thom, C.; Kocienski, P. *Synthesis* **1992**, 582-586.

(19) For a review of thermal reactions utilizing Oppolzer's sultam, see: Kim. B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293-318.

(20) Garner utilized the acrylamide of Oppolzer's sultam for a related dipolar cycloaddition that led to the total synthesis of (–)-quinocarcin, see: Garner, P.; Ho, W.B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742-10753.

(21) The ee of **150** could be raised to >98% by chromatographic purification of **149** prior to the cleavage of the auxiliary.

(22) 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.

(23) Heck coupling reactions between bromide **154** (and the analogous aryl iodide) and enamides such as **147** were also extensively investigated, but these reactions were universally unsuccessful.

(24) For reviews of Suzuki coupling reactions, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

(25) Hydrogenolysis of the benzyl amine proceeded at a rate that was competitive with the rate of olefin hydrogenation. Under conditions with lower hydrogen pressures, a debenzylated compound with the styrene intact could be isolated.

(26) The second product from the hydrogenation in the presence of acetic acid reaction was not fully characterized.

(27) Due to the overlap of key signals in the ^{1}H NMR spectrum, the stereochemistry of **158** was recalcitrant to NOE analysis.

(28) Lemonomycin numbering, see Figure 1.3, Chapter 1.

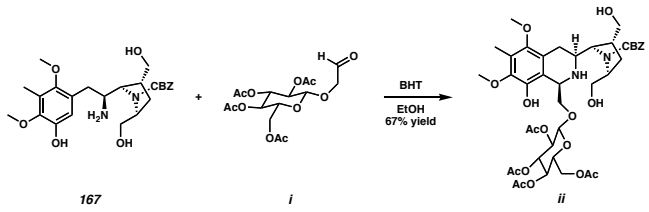
(29) (a) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1907-1910. (b) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1911-1914. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478-2479. (d) Biller, S. A. An Approach to the Total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

(30) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, *5*, 365-368.

(31) Treatment of **165** with trifluoroacetic acid, trimethylsilyl iodide, palladium(0) catalysts, or triphenyl phosphine and carbon tetrabromide failed to yield any cyclized product.

(32) A similar strategy involving reduction of an amide to a primary amine before Pictet-Spengler cyclization was utilized in the Fukuyama synthesis of Saframycin A, see: Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc*. **1990**, *112*, 3712-3713.

(33) *O*-Silyl and *O*-benzyl hydroxyacetaldehyde derivatives were utilized to test the Pictet-Spengler cyclization. As proof of principle for our eventual incorporation of lemonose during the Pictet-Spengler reaction, we also tested the reaction of aminotriol **167** with glucose-derived aldehyde **i**, which provided tetrahydroisoquinoline **ii** in 67% yield.



167 *i* *ii*

(34) The synthesis of lemonose was accomplished in collaboration with Ernie Cruz, a graduate student in the Stoltz research group.

(35) (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367-2371. (b) Szechner, B.; Achmatowicz, O.; Galdecki, Z.; Fruzinski, A. *Tetrahedron* **1994**, *50*, 7611-7624.

(36) This synthetic route was also performed with L-threonine as the starting material, such that both enantiomers of each compound in Scheme 2.15 and Scheme 2.16 have been prepared.

(37) For the synthesis of Weinreb amides from esters with *N*,*O*-dimethylhydroxylamine hydrochloroide and isopropylmagnesium chloride, see: Williams, J. M.; Jobson, R.

B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461-5464.

(38) (a) Chérest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, 2205-2208. (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145-162. (c) Reetz, T. M. *Chem. Rev*. **1999**, *99*, 1121-1162.

(39) The crystal structure shown in Scheme 2.15 was obtained from crystals of *ent*-**175**, which was synthesized from L-threonine. For clarity in this scheme, the obtained structure was inverted to depict the absolute stereochemistry of **175** derived from D-threonine.

(40) The conformation of **178** was minimized by AM1 semiempirical calculations utilizing Spartan '02 v1.0.8 (Wavefunction, Inc.).

(41) An analogous reduction and allyloxy group installation in the absence of the oxazolidine ring provided minimal diastereocontrol over the anomeric center.

(42) For the use of periodate and catalytic osmium tetroxide for the production of carbonyls from alkenes, see: Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem*. **1956**, *21*, 478-479.

(43) Tetrahydroisoquinoline **182** was the only compound recovered from the Pictet-Spengler cyclization. Any trace (<3%) diastereomeric compound arising from the

minor enantiomer of **167** (94% ee) must be removed during HPLC purification of **182**.

(44) The use of glycosyloxy aldehydes in a Pictet-Spengler cyclization is precedented only by our work (see endnote 33). Typical Pictet-Spengler studies have utilized only simple, commercially available aldehydes, see reference 3b.

(45) The mass spectral data of **185** agrees with the proposed structure ($[M+H]^+ = 668.2$), and the ^1H NMR shows an aldehyde peak at 9.65 ppm. However, the compound could not be purified sufficiently to obtain full NMR characterization.

(46) For a review of hypervalent iodine reagents for alcohol oxidation, including the Dess-Martin periodinane, see: Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111-124.

(47) For reviews of alcohol oxidation with activated DMSO reagents, including the Swern, Moffatt, and DMS/NBS oxidations, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857-870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297-572.

(48) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750-6755.

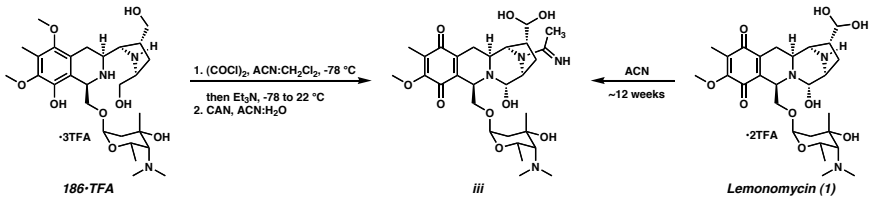
(49) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185-3189.

(50) For a review of tetrapropylammonium perruthenate catalized alcohol oxidation, see: Ley, S. V.; Norman, J. N.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.

(51) Mass spectrometry analysis of the crude reaction mixtures showed M+61 and M+121 in addition to M+H, indicating the presence of one or two methylthiomethyl groups.

(52) In principle, these monooxidized compounds could be resubmitted to the Swern oxidation to yield additional **188**. However, these reactions were not attempted.

(53) In addition to the spectroscopic matching of natural and synthetic (–)-lemonomycin, our synthetic intermediates were chemically correlated with the natural product through a serendipitous discovery. Specifically, Swern oxidation of **186** with acetonitrile as the cosolvent followed by CAN oxidation yielded amidine **iii**, wherein the secondary amine had attacked an equivalent of acetonitrile. Amidine **iii** was also produced when natural (–)-lemonomycin was stored as a solution in acetonitrile for a period of several weeks.



(54) Chiral Lewis acid catalysis has been used for asymmetric dipolar cycloadditions of enal and enoate derivatives. Although this remains an active area of research, we

felt that the use of π-acid catalysis would be more interesting. For recent examples, see: (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926-11927. (b) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001-2004. (c) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6-12. (d) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715-6717. (e) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431-1434. (f) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716-2717.

(55) Organocatalytic nitrone dipolar cycloadditions with enals have also been reported, see: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875. These conditions failed to catalyze the cycloaddition of **146** with acrolein.

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