# CHAPTER FOUR

## Progress Toward The Total Synthesis of (*R*)–Telomestatin[†]

### 4.1 Background

#### 4.1.1 Telomeres and Telomerase

The ends of eukaryotic chromosomes consist of specialized DNA nucleoprotein complexes known as telomeres.[1] Telomeres safeguard the integrity of chromosomes and protect them from base-pair loss, comparable to the small plastic at the end of a shoelace that prevents the twine from unraveling. The human telomere is composed of tandem repeats of the guanine-rich hexanucleotide sequence d(TTAGGG). With the exception of the single-stranded 3′ overhang, most telomeric DNA is double stranded.

In human cells, telomere length erodes naturally with each cell division cycle, since DNA polymerase is unable to fully replicate the ends – a phenomenon known as the "end replication problem". Thus, telomeres are thought to effectively function as cellular clocks, keeping record of how many times a cell divides. Telomeres progressively shorten until a critically short length of telomeric DNA is reached, at which point cells undergo replicative senescence (mortality stage 1 (M1), see Figure 4.1.1), losing their ability to divide.[1] This can be followed by cell crisis (mortality stage 2 ((M2)) and apoptosis.

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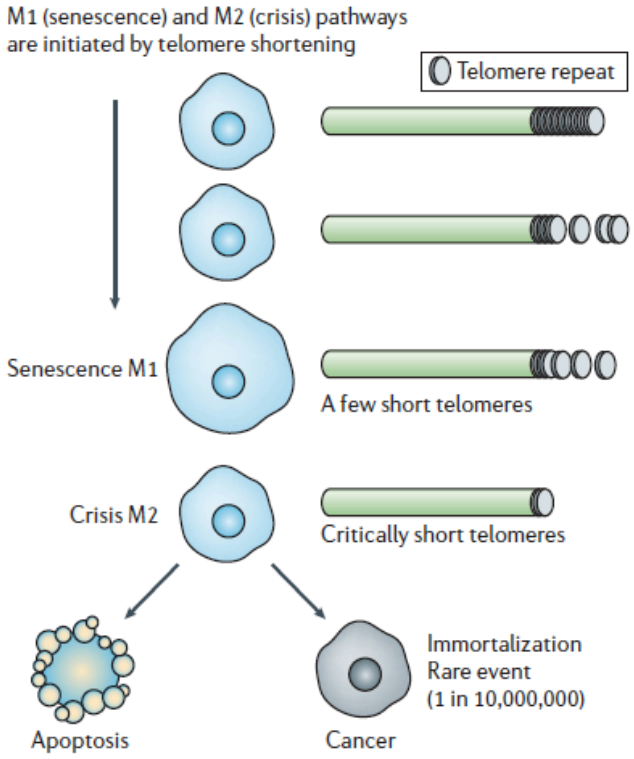
[†] This work was performed in collaboration with Dr. Haiming M. Zhang, a postdoctoral scholar in the Stoltz group, and Justin T. Mohr, a graduate student in the Stoltz group.

*Figure 4.1.1 (reprinted with permission from (2); © 2006, Macmillan Publishers Ltd.)*

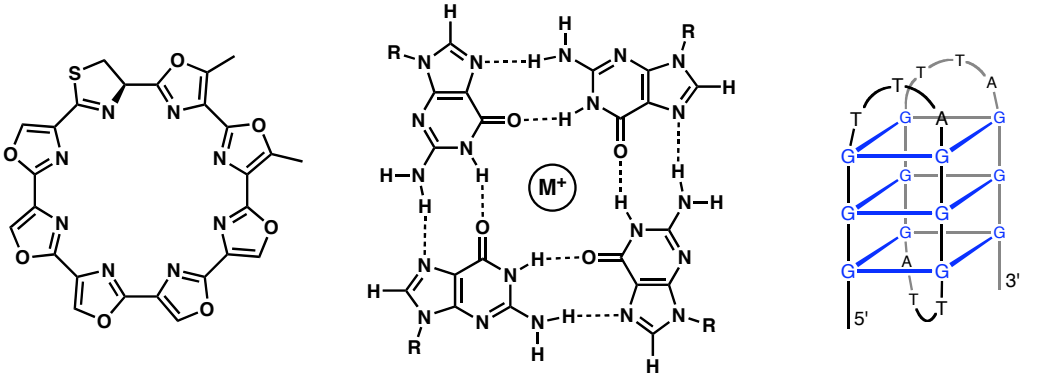



A mechanism for telomere maintenance is provided by a specialized cellular ribonucleoprotein enzyme complex called telomerase.[1,2,3,4,5] Discovered by Carol Greider in 1984, telomerase is involved in telomere capping and in the DNA-damage response, and has been implicated in aging and genetic diseases.[2,3] In human cells, telomerase functions as a reverse transcriptase to add multiple copies of the TTAGGG motif to the end of the G-strand of the telomere. Telomerase activity is usually absent from normal cells; however, in the majority of tumor cells (85-90%) this enzyme is overexpressed, contributing to the immortalization of human tumor cells by protecting against telomere loss during replication.[6] Because telomerase is necessary for the immortality of so many cancer types, telomerase inhibition has become an important target for the development of new anticancer agents.[3]

### 4.1.2 Isolation and Biological Activity

In 2001, a team of Japanese scientists conducted a screen for telomerase inhibitors, and isolated and characterized telomestatin (**189**, Figure 4.1.2) from the metabolites of microorganism *Streptomyces anulatus* 3533-SV4.[7,8,9,10] The structure of telomestatin (**189**) consists of a macrocyclic arrangement of five oxazoles, two methyloxazoles, and one thiazoline ring.[11] Telomestatin (**189**) is the strongest and most specific telomerase inhibitor identified to date, with an $IC_{50}$ value of 0.005 μM (5 nM).[7] Further studies on this natural product demonstrated that it is able to inhibit the activity of telomerase without affecting DNA polymerases or reverse transcriptases.[7]

*Figure 4.1.2*




***Telomestatin (189)*** ***G-Tetrad / G-Quartet (190)*** ***G-Quadruplex (191)***
***Intramolecular Basket-Type***

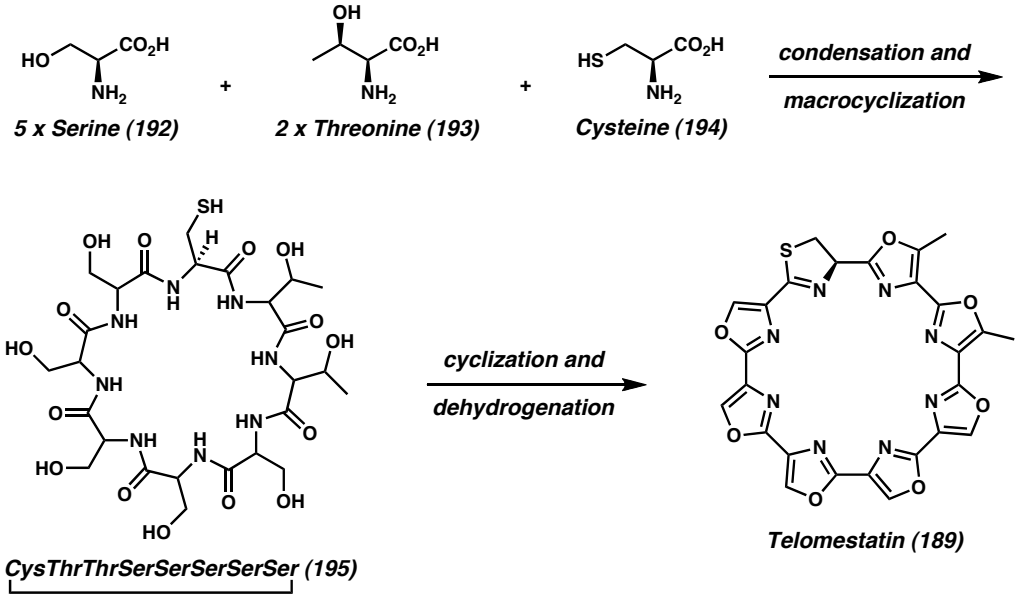
G-quadruplex structures (e.g., **191**) are formed in vivo from the guanine-rich $d(TTAGGG)_n$ repeat sequences of human telomeres, which are stacked layers of G-tetrads (also known as G-quartets, **190**).[12] Previous research has shown that the formation of such G-quadruplex structures (e.g., **191**) sequesters the single-stranded $d(TTAGGG)_n$ primer molecules required for telomerase activity, thus preventing the action of

telomerase.[13] While direct catalytic inhibition of telomerase by telomestatin (**189**) cannot be ruled out, evidence suggests that telomestatin (**189**) facilitates the formation of or stabilizes G-quadruplex structures (e.g., **191**), thereby inhibiting telomerase activity indirectly.[9b,14] Indeed, modeling studies on the binding interactions of telomestatin (**189**) and the G-quadruplex (e.g., **191**) demonstrated that sources of stable interactions include hydrogen bonding between the nitrogens of the guanine bases and the oxygens of the oxazole rings, stacking interactions with the G-tetrad, as well as electrostatic interactions between the ring nitrogens and the guanine bases.[9b]

### 4.1.3 Biosynthesis

The biosynthesis of telomestatin (**189**), although not yet reported in the literature, probably involves the intermediacy of octapeptide **195** generated from the condensation and macrocyclization of eight amino acids—five serine (**192**), two threonine (**193**), and one cysteine (**194**) (Scheme 4.1.1).[15,16] Cyclodehydration and oxidation of **195** would then generate the final product (**189**). Although telomestatin (**189**) is almost certainly derived from the abovementioned amino acids, there is no evidence to suggest that the all of the peptide bonds must be formed prior to the heterocyclization steps.[15a]

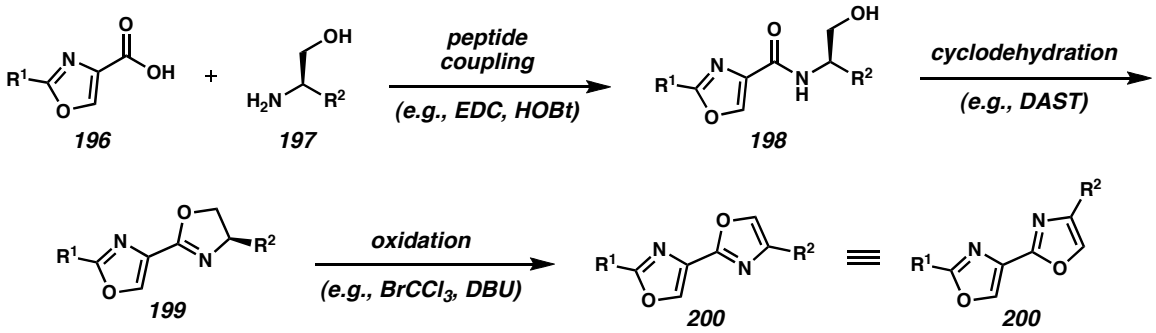
*Scheme 4.1.1*




### 4.1.4 Previous Synthetic Studies

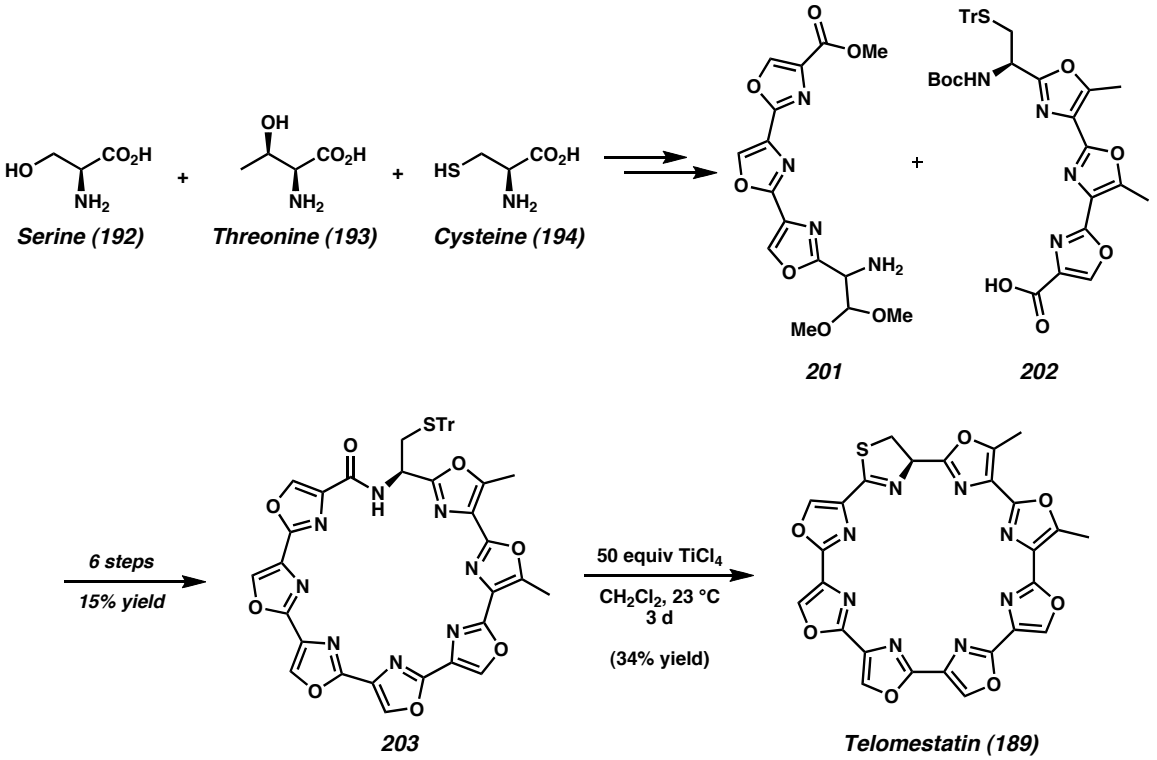
There are two published total syntheses of telomestatin (**189**) in the literature,[17] as well as a handful of syntheses en route to the natural product.[10,18,19] Despite the amount of synthetic attention that this molecule has garnered, however, every one of the reported approaches relies heavily on the use of amino acid precursors, as well as linear, repeated peptide-bond formation–cyclization–oxidation sequences to form the oxazole rings (**196** + **197** → **198** → **199** → **200**, Scheme 4.1.2). In fact, this sequence bears resemblance to the proposed telomestatin (**189**) biosynthesis (Scheme 4.1.1, vide infra). Not surprisingly, the use of these methods typically also requires multiple protection and deprotection steps. While the described routes are usually reasonably convergent, the use of this inefficient design strategy (i.e., Scheme 4.1.2) renders them lengthy and impractical—especially for analog synthesis.

*Scheme 4.1.2*



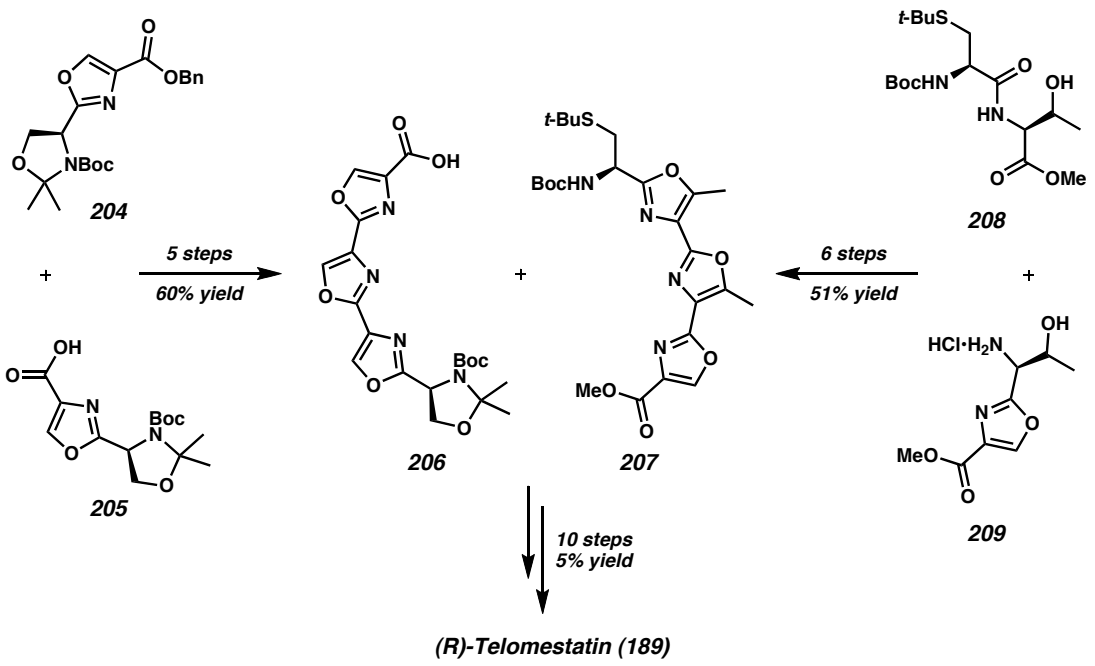

The first total synthesis of telomestatin (**189**) appeared in the literature in a 2002 patent reported by the Japanese company Taiho Pharmaceutical (Scheme 4.1.3).[17a] While experimental details are limited, they achieved the synthesis of **201** and **202** in unreported yields via the use of peptide bond formation–cyclization–oxidation sequences beginning from amino acid precursors (**192**–**194**, see Scheme 4.1.2, vide infra). Trisoxazole ester **201** and trisoxazole acid **202** were then stitched together in a similar manner over 6 steps to form **203**, and $TiCl_4$-mediated thiazoline closure produced the natural product (**189**). Advancing the two key trisoxazole fragments (**201** and **202**) to the end required 7 total steps in 5% overall yield, with 10 mg of the natural product reported.

*Scheme 4.1.3*




During the course of our synthetic endeavors, a Japanese group led by Doi and Takahashi also reported a total synthesis of telomestatin (**189**), and definitively confirmed the absolute stereochemistry of the natural product as (*R*)-telomestatin (**189**).[17b] Although the details of the Taiho Pharmaceutical synthesis are incomplete,[17a] both of these routes appear to be fundamentally similar (Scheme 4.1.4). Amino-acid-derived building blocks **204**, **205**, **208**, and **209** were readily available in less than 5 steps, and could be advanced to key trisoxazole fragments **206** and **207** using the cyclization protocol previously described (see Scheme 4.1.2, vide infra). These two key fragments (**206** and **207**) were then advanced over 10 subsequent steps to provide the natural product in 5% overall yield from these intermediates.

*Scheme 4.1.4*




In addition to the aforementioned synthetic efforts, a handful of novel poly-oxazole methodologies have also been published. These methods include a two-stage iterative oxazole synthesis by Vedejs,[20a] as well as a series of palladium-catalyzed Suzuki coupling approaches by Greaney and Inoue.[20b–d] While these approaches seem promising, to date they have not been resulted in a completed total synthesis of telomestatin (**189**).

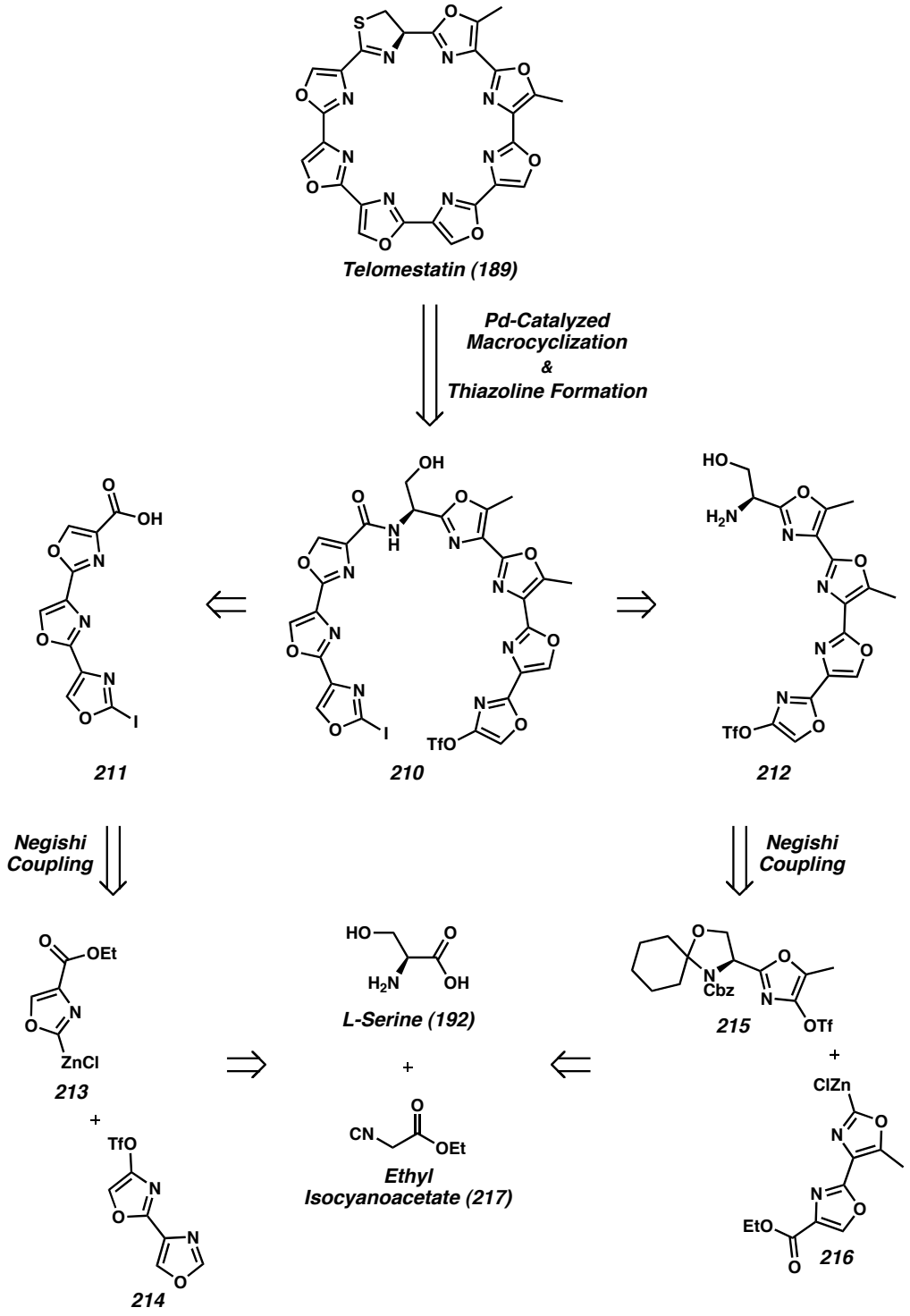
Given the significant anticancer therapeutic potential of telomestatin (**189**),[9,10] as well as the lengthy and low-yielding preparations to date,[17] a successful synthesis of this molecule would not only deliver the natural product in an efficient manner, but would also be readily amenable to analog synthesis for further biological testing.

### 4.1.5 Retrosynthetic Analysis of Telomestatin

Our retrosynthetic analysis for telomestatin (**189**) is shown in Scheme 4.1.5. On the basis of the reported telomestatin (**189**) syntheses,[17] as well as the potential for sulfur to oxidize or poison metal catalysts, we envisioned a late-stage installation of the sulfur moiety and the thiazoline ring. Additionally, in order to maximize synthetic efficiency, we sought to complete the final aryl–aryl linkage of **210** and induce macrocyclization using a palladium-catalyzed cross-coupling.[21,22] This maneuver would also allow for a high degree of convergency by dividing the molecule into two roughly equal halves.[23] Disconnection across the amide bond in **210** then reveals trisoxazole iodo acid **211** and tetrakisoxazole amino alcohol **212**.

Iodo acid **211** would be targeted by way of a palladium-catalyzed Negishi cross-coupling between zinc reagent **213** and bisoxazole triflate **214**. Amino alcohol **212**, in turn, would also be assembled using a Negishi cross-coupling between triflate **215** and zinc reagent **216**. All of the achiral oxazole building blocks (**213**, **214**, **216**) would be obtained from ethyl isocyanoacetate (**217**), and chiral triflate **215** would be derived from the natural amino acid *L*-serine (**192**).

*Scheme 4.1.5*

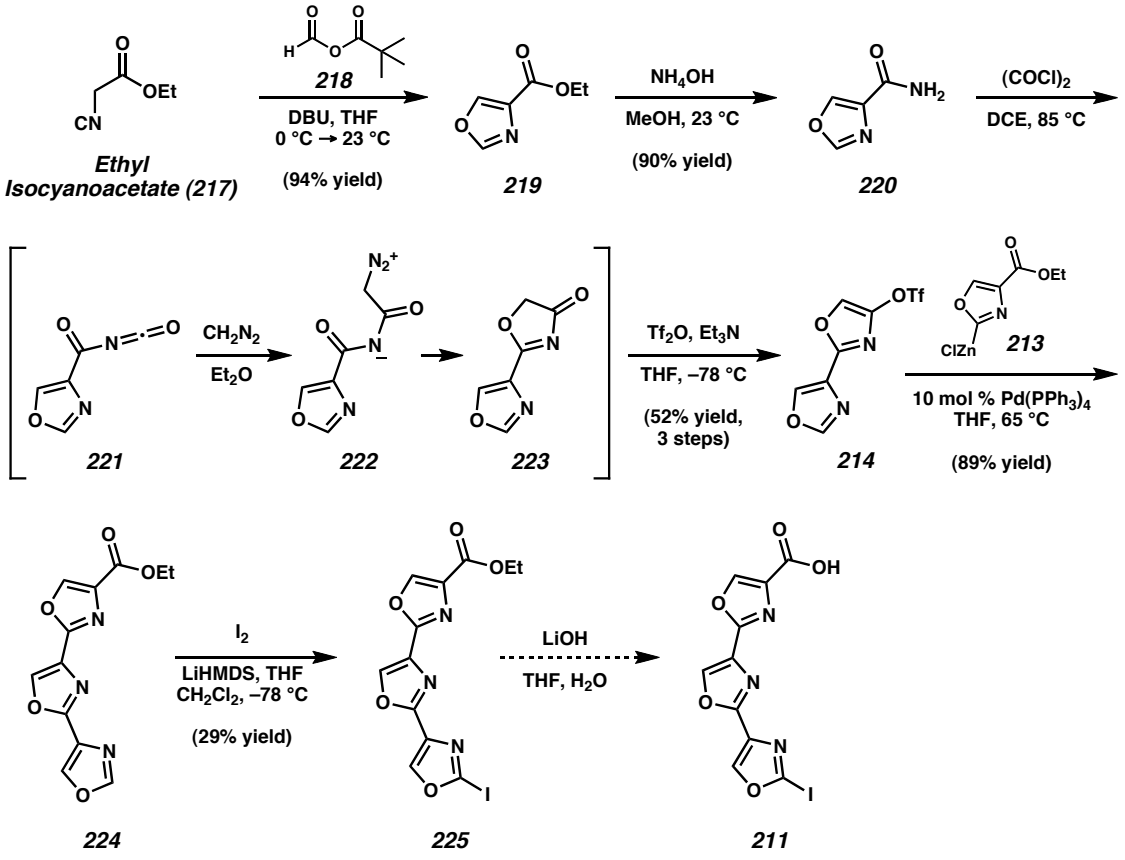

Telomestatin (189)
Pd-Catalyzed Macrocyclization & Thiazoline Formation
211
210
212
Negishi Coupling
Negishi Coupling
213
214
L-Serine (192)
Ethyl Isocyanoacetate (217)
215
216

## 4.2 Progress Toward The Total Synthesis of Telomestatin

### 4.2.1 Synthesis of Left-hand Trisoxazole Iodo Acid

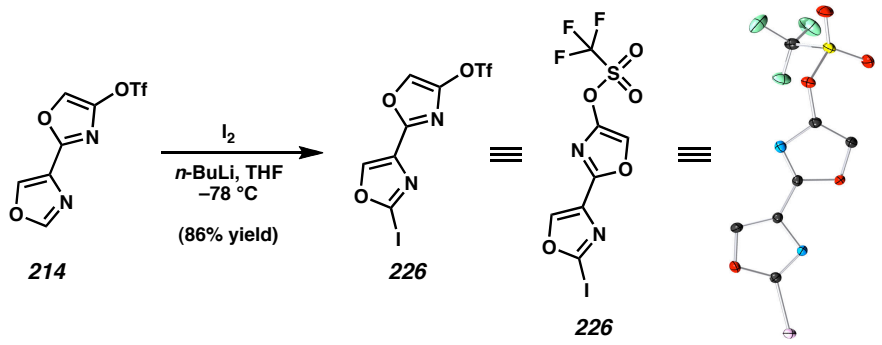
Our synthesis of the left-hand trisoxazole portion (**211**) of telomestatin (**189**) began with the preparation of known oxazole ester **219**. Exposure of ethyl isocyanoacetate (**217**) to mixed anhydride **218**[24] and DBU led to a high yield of oxazole ester **219**,[25] which was smoothly converted to amide **220** by the action of aqueous ammonia in methanol (Scheme 4.2.1). Conversion to bisoxazole triflate **214** was achieved by means of a three-step sequence, which commenced by heating amide **220** in the presence of oxalyl chloride to give rise to acyl isocyanate **221**.

*Scheme 4.2.1*



Subjection of acyl isocyanate **221** to anhydrous, alcohol-free diazomethane dried over sodium metal[26] led to in situ production of **222**, which rapidly cyclized with loss of nitrogen to form oxazolone **223**.[27] Treatment of this intermediate with $Tf_2O$ and amine base produced bisoxazole triflate **214** in 52% yield over 3 steps.[28] Although NMR techniques were initially used for characterization, further confirmation of the structural identity was achieved by single crystal X-ray diffraction upon conversion to the iodo derivative (**214** → **226**, Scheme 4.2.2).[29]

*Scheme 4.2.2*



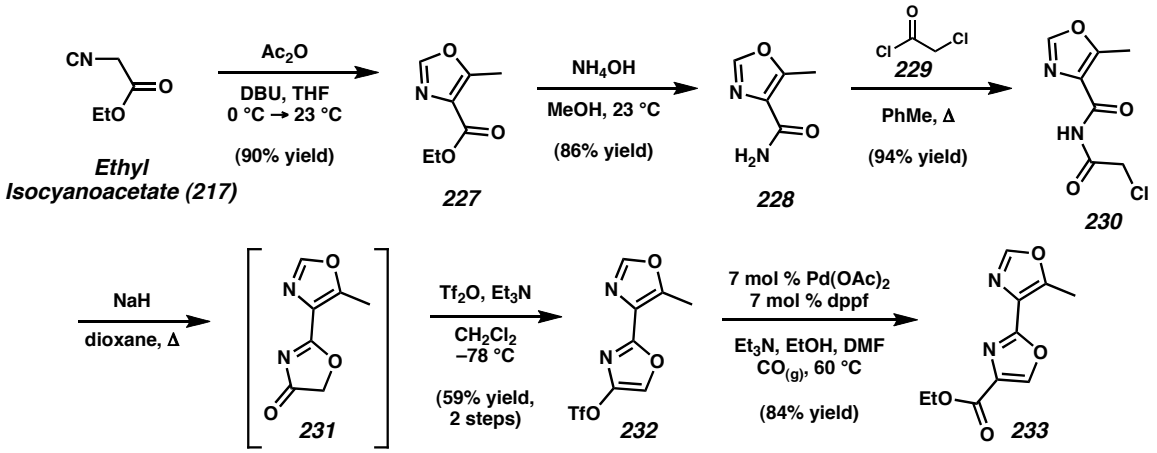

A wide range of cross-couplings of appropriate mono and bisoxazole subunits were investigated to prepare the desired trisoxazole fragment (**224**), including Stille, Suzuki, and Negishi protocols.[30,31] Ultimately, the Negishi approach proved to be the most robust to accomplish this union.[30] The necessary zinc reagent (**213**) for this reaction could be prepared from **219** via a deprotonation/quenching event with LiHMDS and $ZnCl_2$, furnishing trisoxazole **224** after successful aryl fusion with bisoxazole **214**.[32] Installation of the heteroaryl iodide could be realized at this juncture, since incorporating the iodide earlier in the synthesis would likely interfere with the Negishi cross-coupling

of **214** + **213**.[33] Deprotonation of trisoxazole **224** using LiHMDS, in an optimized solvent mixture of THF and dichloromethane,[34] followed by quenching with iodine produced **225**.[32] Finally, it is anticipated that hydrolysis of ester **225** would lead to the desired acid (**211**).

### 4.2.2 Synthesis of Right-hand Tetrakisoxazole Amino Alcohol

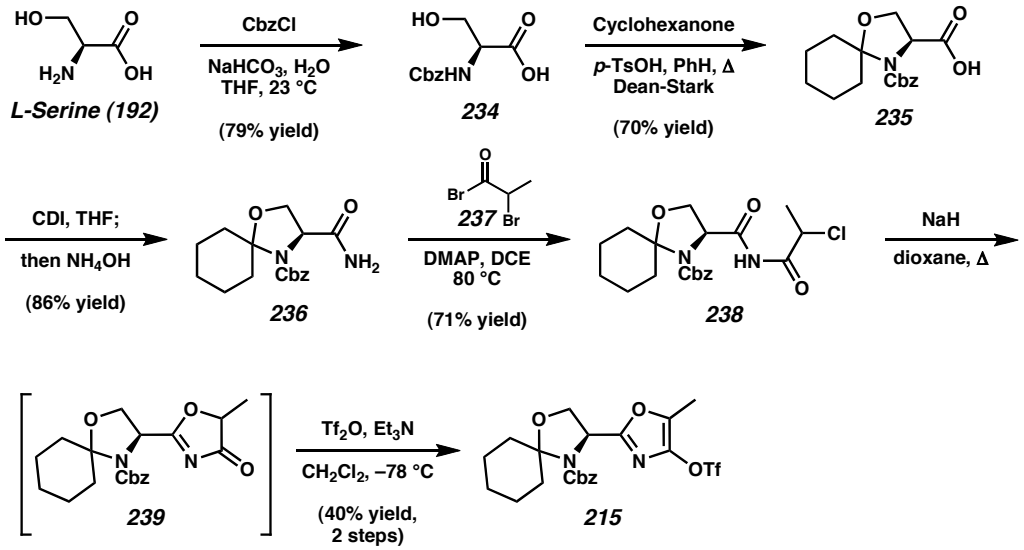
Assembly of the tetrakisoxazole amino alcohol subunit (**212**) begins with the preparation of methylbisoxazole ester **233**. The synthesis of this fragment is adapted from the route to bisoxazole triflate **214** (see Scheme 4.2.1, vide infra). Following a reported two-step procedure, mixing ethyl isocyanoacetate (**217**) with acetic anhydride and DBU led to the formation of methyloxazole ester **227**,[35] which was treated with ammonium hydroxide to generate amide **228** (Scheme 4.2.3). Acetylation with chloroacetyl chloride (**229**) gave rise to imide **230**, which could be converted to triflate **232** via oxazolone **231**. A Pd-catalyzed carbonylation reaction of triflate **232** with ethanol led to the production of desired ester **233** in 84% yield.

*Scheme 4.2.3*



With ester **233** now in hand, preparation of the triflate coupling partner (**215**) could proceed. Protection of *L*-serine (**192**) as the *N*-Cbz carbamate (**234**) was accomplished using published procedures (Scheme 4.2.4).[36] Refluxing **234** under Dean-Stark conditions with cyclohexanone and a catalytic amount of *p*-toluenesulfonic acid afforded cyclohexylidene **235**.[37] Acid **235** was then activated with CDI, and displaced with $NH_4OH$ to produce amide **236**. Reaction of amide **236** with **237** led to imide cyclization precursor **238**, which was treated with NaH to form oxazolone **239**. Finally, oxazole triflate **215** was accessed from oxazolone **239** via triflation.

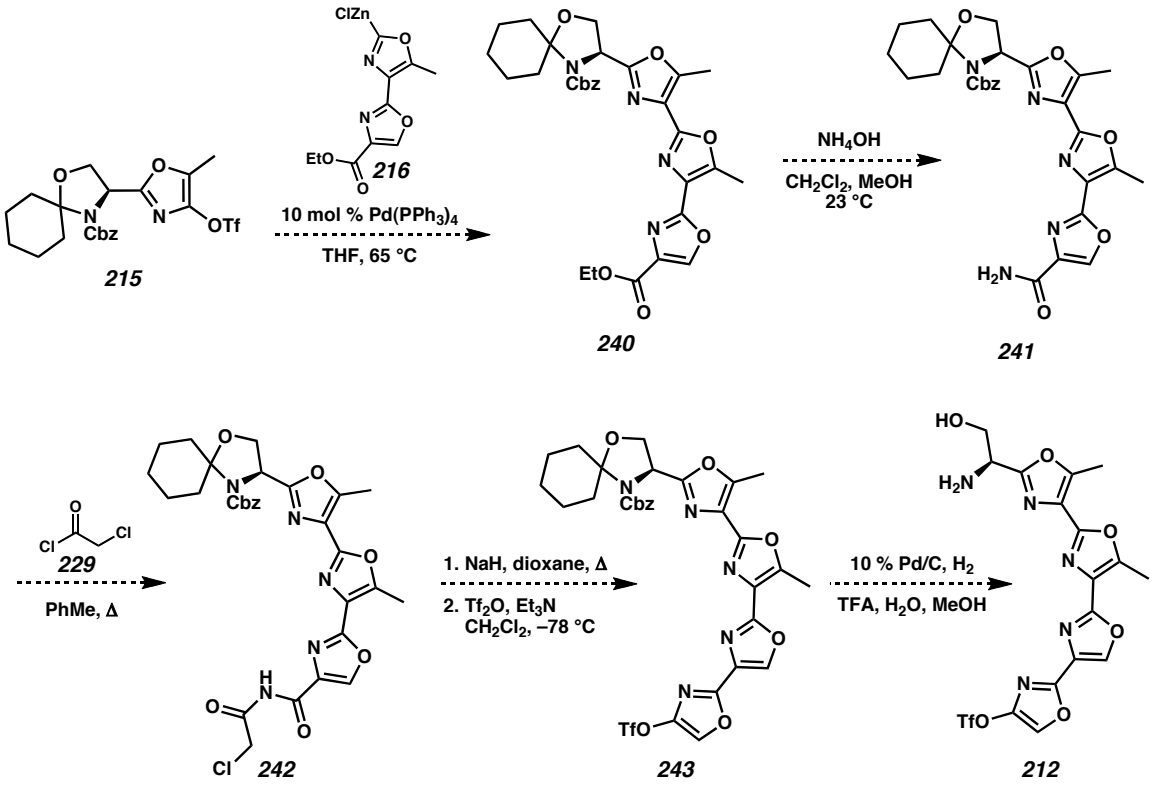
*Scheme 4.2.4*




With the ready availability of the key coupling partners (**215** and **233**), the Negishi cross-coupling was attempted. It is anticipated that exposure of triflate **215** to the Negishi reagent (**216**) of ester **233** under palladium catalysis would lead to the assembly of trisoxazole **240** (Scheme 4.2.5).[38] Installation of the final oxazole ring present in

desired tetrakisoxazole **212** could then be initiated via conversion to amide **241**. Acylation of amide **241** would then be executed to prepare imide **242**, which could be cyclized and treated with $Tf_2O$ to furnish tetrakisoxazole triflate **243**.[39] Cleavage of both the benzyl carbamate and cyclohexylidene protecting groups would then occur under the action of Pd/C, $H_2$, and TFA in wet methanol, ultimately affording amino alcohol **212**.[40]

*Scheme 4.2.5*

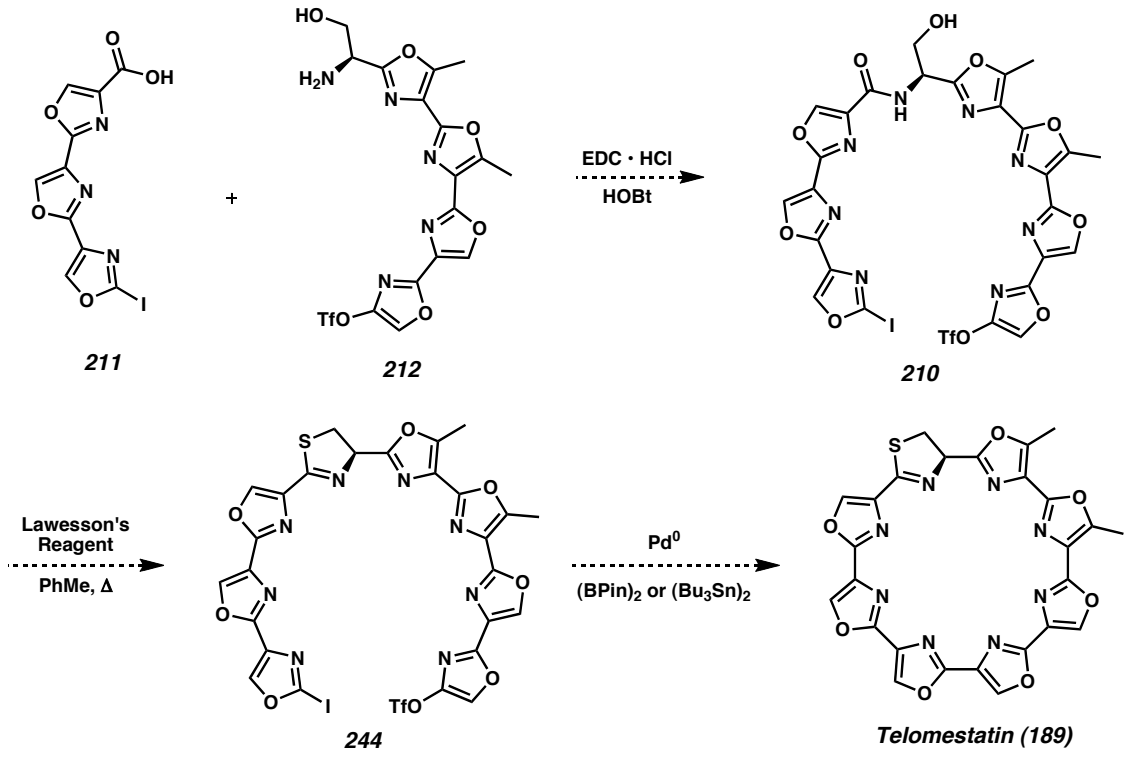



### 4.2.3 Late-Stage and Proposed Endgame

With the assembly of the two major fragments completed (**211** and **212**), amide bond formation would then be initiated (Scheme 4.2.6). Successful coupling of these two partners would afford hydroxyamide **210**. Treatment of **210** with Lawesson's reagent is

then anticipated to lead to closure of the thiazoline ring to form **244**.[41] Finally, an intramolecular Pd-catalyzed cross-coupling of the iodide and triflate moieties of **244** would complete the macrocycle, as well as the total synthesis of telomestatin (**189**).[21,42,43,44]

*Scheme 4.2.6*




## 4.3 Conclusion

In conclusion, we have developed an extremely promising route to deliver the potent telomerase inhibitor (*R*)-telomestatin (**189**) from readily available ethyl isocyanoacetate (**217**) and *L*-serine (**192**). Our convergent synthesis employs palladium-mediated cross-coupling reactions to assemble oligooxazole intermediates from oxazole

building blocks. Additionally, this strategy utilizes a minimum number of protecting groups, and proposes a unique aryl–aryl macrocyclization as the last step of the synthesis.

In addition to the biological relevance of the desired target, a successful total synthesis of telomestatin using our approach would also enable rapid access to the preparation of telomestatin analogs. This would allow for the investigation of key interactions between telomestatin and the G-quadruplex, as well as the examination of the predictions generated by previous computer modeling studies, especially the still unresolved question of whether telomestatin actually facilitates the formation of the G-quadruplex, stabilizes the G-quadruplex, or does both.

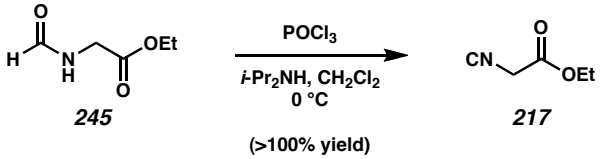
## 4.4 Experimental Section

### 4.4.1 Materials and Methods

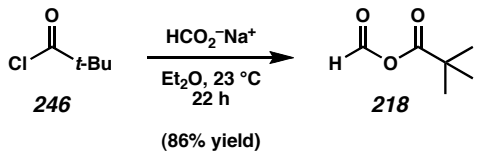
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) or SiliCycle Silia*Flash* P60 Academic silica gel (particle size 0.040–0.063 mm; pore diameter 60 Å) was used for flash column chromatography. $^{1}$H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), or a Varian Inova 500 (at 500 MHz) 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. $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to $Me_4Si$ (δ 0.0). Data for $^{13}$C NMR spectra are reported in terms of chemical shift (δ ppm) and coupling constant ($^{19}$F, Hz). $^{19}$F NMR spectra were recorded on a Varian Mercury 300 (at 282 MHz) and are reported relative to external $F_3CCO_2H$ standard (δ –76.53). Data for $^{19}$F NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained

from the California Institute of Technology Mass Spectral Facility. X-Ray crystallographic data were obtained from the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory.

### 4.4.2 Preparative Procedures

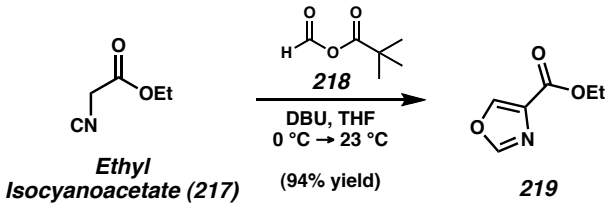



**Ethyl Isocyanoacetate (217).** To a solution of *N*-formylglycine ethyl ester (**245**, 52.9 mL, 403.4 mmol) in $CH_2Cl_2$ (330 mL) at 0 °C was added *i*-$Pr_2NH$ (142 mL, 1.013 mol). $POCl_3$ (41.0 mL, 447.9 mmol) was added dropwise over 1 h (1 drop/s addition rate). The reaction was stirred for 3 h at 0 °C, then quenched by slow addition of $Na_2CO_3$ (90.0 g in 400 mL $H_2O$), keeping the internal temperature below 15 °C. After the addition was complete, the reaction was stirred for 2 h at 23 °C. $CH_2Cl_2$ (500 mL) and $H_2O$ (400 mL) were added, and the phases were partitioned. The aqueous layer was further extracted with $CH_2Cl_2$ (2 x 250 mL). The organic layers were combined, washed with $H_2O$ (200 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo to furnish ethyl isocyanoacetate (**217**, 46.2 g, 45.6 g theoretical, >100% yield) as an orange oil. This crude material was used without any further purification. $R_f$ 0.61 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, $J$ = 7.1 Hz, 2H), 4.20 (s, 2H), 1.31 (t, $J$ = 7.2 Hz, 3H). This compound is also commercially available from Aldrich (226319).




**Mixed Anhydride 218.**[24] To a suspension of finely powdered oven-dried sodium formate (63.78 g, 937.9 mmol) in $Et_2O$ (590 mL) was added pivaloyl chloride (**246**, 57.7 mL, 468.7 mmol) over 2 min. The suspension was vigorously stirred at 23 °C for 22 h. The solid was removed by filtration, and the filtrate was evaporated in vacuo at 0 °C, affording mixed anhydride **218** (52.3 g, 86% yield) as a volatile, colorless oil. This material was immediately used in the next step without further purification. Characterization data for this compound have been previously reported.[24]

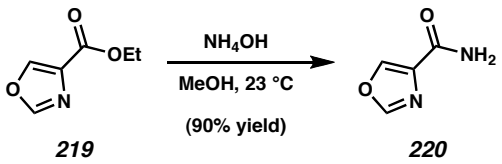
*NOTE: The rate of this heterogeneous reaction seems to be dependent on the particle size of sodium formate as well as the stirring rate. It is highly advised to monitor the reaction by $^1H$ NMR until the pivaloyl chloride (**246**) is consumed.*




**Oxazole Ester 219.**[25] To a stirring solution of ethyl isocyanoacetate (**217**, 5.74 g, 5.54 mL, 50.7 mmol) in THF (60 mL) at 0 °C was added DBU (15.2 mL, 101.6 mmol), followed by a solution of mixed anhydride **218** (13.2 g, 101.4 mmol) in THF (40 mL) added over 5 min. The mixture was stirred at 0 °C for 30 min, and then at 23 °C for 15 h. The reaction mixture was concentrated, and the crude product was filtered over a plug of silica gel (1:1 hexanes:EtOAc eluent). The solvent was evaporated under reduced

pressure, and the residue was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to afford oxazole ester **219** (6.44 g, 90% yield) as a yellow oil, which solidified upon refrigeration.

*Alternate Procedure*. To a solution of ethyl isocyanoacetate (**217**, 22.4 g, 197.6 mmol) in THF (221 mL) at 0 °C was added DBU (60.0 mL, 401.2 mmol), followed by additional THF (30 mL). To this solution was added freshly prepared mixed anhydride **218** (51.7 g, 397.5 mmol) in THF (120 mL) via cannula over 25 min at 0 °C, followed by additional THF (40 mL). The reaction was stirred for 4 h, and the temperature was allowed to increase gradually from 0 °C → 23 °C. EtOAc (255 mL) and $H_2O$ (130 mL) were added, and the phases were partitioned. The aqueous layer was further extracted with EtOAc (3 x 250 mL). The organic layers were combined and washed with 0.5 M HCl (2 x 100 mL), saturated aq. $Na_2CO_3$ (100 mL), $H_2O$ (100 mL), and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to yield a dark, orange oil. The crude product was purified by passage over a plug of silica gel (1:1 hexanes:EtOAc eluent) to provide oxazole ester **219** (14.80 g, 53% yield) as a yellow oil. $R_f$ 0.43 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J$ = 0.8 Hz, 1H), 7.91 (d, $J$ = 0.8 Hz, 1H), 4.38 (q, $J$ = 7.2 Hz, 2H), 1.37 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.2, 151.6, 144.2, 133.6, 61.5, 14.5; IR (film) 3131, 2983, 1740, 1312, 1148, 1102 cm$^{-1}$; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_6H_7NO_3$, 141.0426; found, 141.0423.

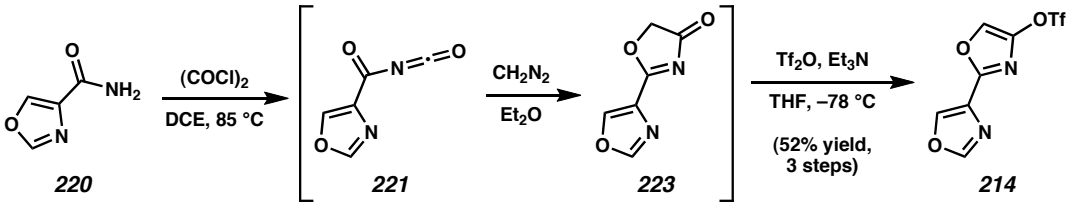



*219* *220*

**Oxazole Amide 220.** To a solution of oxazole ester **219** (1.41 g, 10.0 mmol) in MeOH (25 mL) was added concentrated ammonium hydroxide (28.0–30.0% in $H_2O$, 25 mL) in one portion at 23 °C. After stirring at 23 °C for 3 h, the solvent was evaporated in vacuo. The crude product was adsorbed onto silica gel using MeOH as solvent, and purified by flash chromatography (10:1 $CHCl_3$:MeOH eluent) to furnish amide **220** (1.02 g, 90% yield) as a white solid.

*Alternate Procedure*. To a solution of oxazole ester **219** (28.92 g, 204.9 mmol) in MeOH (134 mL) was added concentrated ammonium hydroxide (28–30%, 127 mL) in one portion at 23 °C. The reaction was stirred for 11 h at 23 °C, and then the solvent was evaporated in vacuo. Following further coevaporation under reduced pressure with acetonitrile (3 x 150 mL), the crude product was dissolved in boiling EtOAc (750 mL). Solid impurities were removed by decantation, and the solution was allowed to cool to 23 °C. Hexanes (1 L) was added, and the solution was cooled to 12 °C and allowed to crystallize. The product was collected by vacuum filtration and dried further under high vac to yield oxazole amide **220** (14.30 g, 62% yield) as a pale yellow solid. The filtrate was concentrated, and the crystallization procedure was repeated to afford a second batch of **220** (3.59 g), which was combined with the first batch to provide oxazole amide **220** (17.89 g, 78% combined yield) as a pale yellow solid. $R_f$ 0.35 (10:1 $CHCl_3$:MeOH); mp 156–158 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.56 (d, $J$ = 1.1 Hz, 1H), 8.48 (d, $J$ = 1.1 Hz, 1H), 7.66 (br s, 1H), 7.51 (br s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 161.8, 152.2,

142.0, 135.8; IR (KBr) 3379, 3154, 3111, 1664 (br), 1413, 1111 $cm^{-1}$; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_4H_4N_2O_2$, 112.0273; found, 112.0271.



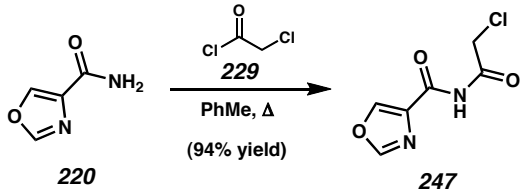

**Bisoxazole Triflate 214.** To oxazole amide **220** (224.0 mg, 2.0 mmol) and 1,2-dichloroethane (20 mL) in a Schlenk flask at 23 °C was added $(COCl)_2$ (0.720 mL, 8.25 mmol) in a rapid dropwise fashion. The flask was sealed, and the mixture was heated at 85 °C for 2 h. The reaction was allowed to cool to 23 °C, and the solvent was carefully evaporated in vacuo under an inert atmosphere to afford **221** as a pale yellow solid, which was immediately used in the subsequent reaction without further purification.

To crude acylisocyanate **221** dissolved in $Et_2O$ (20 mL) was added a sodium-dried ethanol-free solution of freshly prepared $CH_2N_2$ in $Et_2O$[26] (20 mL) in a rapid dropwise fashion. When bubbling ceased, and the solution turned pale yellow, the solvent was carefully concentrated in vacuo under an inert atmosphere to afford crude oxazolone **223** as a yellow solid, which was directly used in the following step.

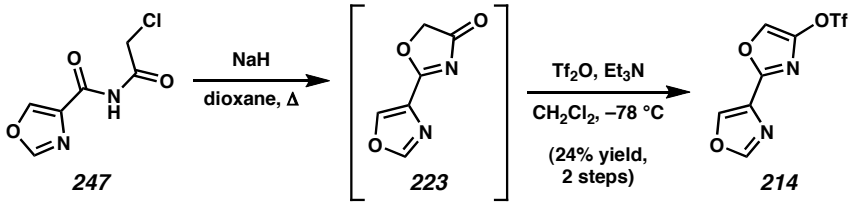
To oxazolone **223** in THF (30 mL) at –78 °C was added $Et_3N$ (0.700 mL, 5.02 mmol), followed by dropwise addition of $Tf_2O$ (0.512 mL, 3.04 mmol). The reaction was stirred at –78 °C for 1 h, and allowed to thaw at 23 °C for 30 min. $Et_2O$ (30 mL) was then added, and the precipitates were removed by vacuum filtration. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford bisoxazole triflate **214** (298.0 mg, 52% yield, 3 steps) as

a yellow oil, which solidified upon refrigeration. $R_f$ 0.64 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, $J$ = 0.8 Hz, 1H), 8.00 (d, $J$ = 0.8 Hz, 1H), 7.75 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.3, 145.8, 140.0, 129.7, 126.9, 118.8 (q, $J_{CF}$ = 320 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –73.2; IR (film) 3133, 1585, 1429, 1215, 1131 cm$^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_3N_2O_5F_3S$, 283.9715; found, 283.9707.

*Alternate procedure for the preparation of **214**:*



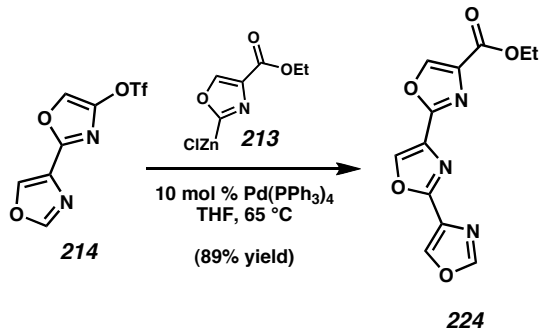

**Oxazole Chloro Imide 247.** To a suspension of oxazole amide **220** (3.20 g, 28.6 mmol) in toluene (30 mL) was added chloroacetyl chloride (**229**, 3.0 mL, 37.7 mmol) over 30 sec at 23 °C. The flask was fitted with reflux condenser and a drying tube containing Drierite®, and the reaction mixture was heated at 115 °C for 4.5 h under gentle reflux. The reaction was allowed to cool to 23 °C, and hexanes (150 mL) was added. After cooling to 0 °C, the product was collected by vacuum filtration, washed with hexanes (3 x 30 mL), and further dried under high vac to furnish oxazole imide **247** (5.04 g, 94% yield) as a light brown powder. $R_f$ 0.33 (1:1 hexanes:EtOAc); mp 126–128 °C; $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 11.06 (br s, 1H), 8.97 (d, $J$ = 1.1 Hz, 1H), 8.62 (d, $J$ = 1.1 Hz, 1H), 4.73 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 167.5, 158.9, 152.8, 144.9, 133.9, 45.5; IR (KBr) 3307, 3139, 1734, 1700, 1578, 1471, 1287, 1188, 1095, 1050 cm$^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_6H_5N_2O_3Cl$, 187.9989; found, 187.9992.




**Bisoxazole Triflate 214.** To a whipped suspension of NaH (60% dispersion in mineral oil, 1.81 g, 45.3 mmol) in dioxane (725 mL) at 23 °C was added oxazole imide **247** (8.00 g, 42.4 mmol) portionwise over 1 min. The mixture was stirred at 23 °C for 15 min and then was heated at 110 °C for 40 min. After cooling to 23 °C over 1 h, the reaction mixture was filtered over a pad of Celite® ($Et_2O$ eluent). The filtrate was coevaporated under reduced pressure with heptane (3 x 500 mL) and benzene (300 mL), and was further dried under high vac to provide oxazolone **223** as an orange solid. This material was immediately carried to the subsequent step without further purification. Although oxazolone **223** is typically used in crude form, it has been observed by $^1$H NMR. $^1$H NMR (300 MHz, DMSO-$d_6$) δ (9.31, $J$ = 0.9 Hz, 1H), 8.75 (d, $J$ = 0.9 Hz, 1H), 4.91 (s, 2H).

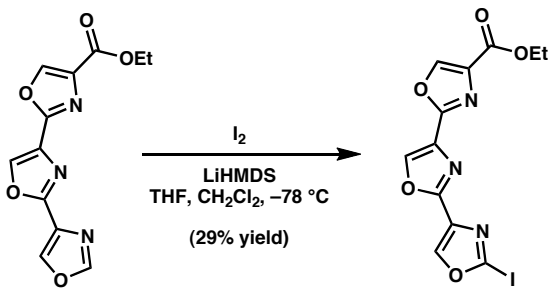
To oxazolone **223** dissolved in $CH_2Cl_2$ (230 mL) at –78 °C was added $Et_3N$ (12.0 mL, 86.1 mmol) over 1 min, followed by dropwise addition of freshly prepared $Tf_2O$ (8.6 mL, 51.1 mmol) over 2 min. The reaction was held at –78 °C for 45 min, and was then immediately warmed to 0 °C for 15 min. $H_2O$ (100 mL) was added, and the phases were partitioned. The aqueous phase was further extracted with $CH_2Cl_2$ (2 x 300 mL), and the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford a dark colored syrup. The residue was purified by flash chromatography (7:3 hexanes:$CH_2Cl_2$ → 1:1 hexanes:$CH_2Cl_2$ eluent), and the product-containing fractions were collected and concentrated in vacuo. The crude product was further purified by flash

chromatography (4:1 hexanes:EtOAc eluent) to afford bisoxazole triflate **214** (2.927 g, 24% yield, 2 steps) as an off-white solid.




**Trisoxazole Ester 224.** To oxazole ester **219** (155.2 mg, 1.10 mmol) in THF (9.5 mL) at –78 °C was added LiHMDS (1.0 M in THF, 1.23 mL, 1.23 mmol) in a dropwise fashion. The reaction was stirred at –78 °C for 30 min, and then $ZnCl_2$ (0.5 M in THF, 6.70 mL, 3.35 mmol) was added over 3 min. The solution was kept at –78 °C for an additional 5 min and was then held at 0 °C for 2.5 h to deliver Negishi reagent **213**. In a separate flask was prepared a solution of bisoxazole triflate **214** (267.8 mg, 0.94 mmol), $Pd(PPh_3)_4$ (109.5 mg, 0.09 mmol), and THF (9.5 mL). This freshly prepared solution was then transferred into the flask containing Negishi reagent **213** via cannula, and the resulting mixture was heated at 65 °C for 1.5 h. After cooling to 23 °C, the reaction mixture was diluted with $CH_2Cl_2$ (30 mL) and filtered over a plug of silica gel (1:1 hexanes:EtOAc → EtOAc eluent). The product containing-fractions were concentrated under reduced pressure, adsorbed onto silica gel using a 1:1 mixture of THF:$CH_2Cl_2$ as solvent, and purified further by flash chromatography (3:1 hexanes:EtOAc → EtOAc eluent). The product-containing fractions were concentrated in vacuo and redissolved in a minimum of hot $CH_2Cl_2$:THF (1:1, 4 mL). Hexanes (12 mL) was added, and the

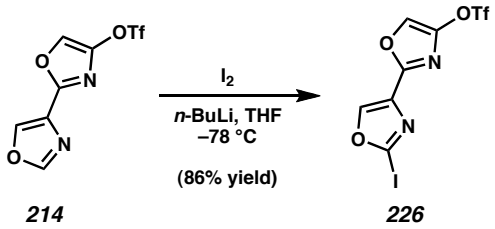
suspension was stirred for 2 h. The solvent was carefully removed, and the solid was triturated with hexanes (2 x 10 mL). The solid was dried under high vac to provide trisoxazole ester **224** (230.4 mg, 89% yield) as a fluffy, white solid. $R_f$ 0.31 (3:1 EtOAc:hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.10 (s, 1H), 9.05 (d, $J$ = 1.1 Hz, 1H), 8.99 (s, 1H), 8.68 (d, $J$ = 0.8 Hz, 1H), 4.32 (q, $J$ = 7.2 Hz, 2H), 1.31 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 160.4, 155.6, 154.9, 153.6, 145.6, 141.1, 141.0, 133.5, 130.0, 128.5, 60.8, 14.1; IR (film) 3136, 1721, 1277, 1164 cm$^{-1}$; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{12}H_{10}N_3O_5$, 276.0620; found, 276.0629.




***224*** ***225***

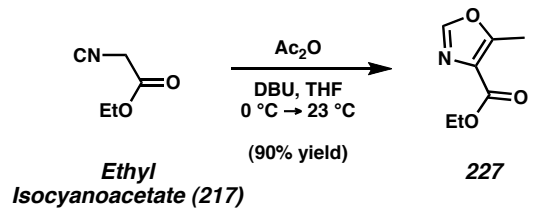
**Trisoxazole Iodo Ester 225.** To trisoxazole ester **224** (100.1 mg, 0.37 mmol) in THF (24 mL) and $CH_2Cl_2$ (13 mL) at –78 °C was added LiHMDS (1.0 M in THF, 440 μL, 0.44 mmol) dropwise. The reaction was stirred for 30 min at –78 °C, and then a solution of $I_2$ (138.6 mg, 0.55 mmol) in THF (2.0 mL) was added in a rapid dropwise fashion. The solution was allowed to warm slowly to 23 °C over 3 h and then was concentrated in vacuo. The residue was dissolved in a minimum of THF:$CH_2Cl_2$ (1:1, 7 mL) and was filtered over a plug of silica gel (1:1 EtOAc:$CH_2Cl_2$ eluent). The product-containing fractions were concentrated and purified by flash chromatography (6:4 $CH_2Cl_2$:EtOAc eluent). The solid residue was suspended in THF:$CH_2Cl_2$ (1:1, 4 mL) and

hexanes (10 mL) and vigorously triturated. Further trituration with hexanes (2 x 10 mL) and drying under high vac afforded trisoxazole iodo ester **225** (42.3 mg, 29% yield) as a yellow solid. $R_f$ 0.35 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.12 (s, 1H), 9.10 (s, 1H), 9.00 (s, 1H), 4.32 (q, $J$ = 7.1 Hz, 2H), 1.31 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 160.4, 154.8, 154.7, 146.2, 145.6, 141.1, 133.5, 131.5, 130.0, 109.3, 60.8, 14.1; IR (film) 3132, 1720, 1133 cm$^{-1}$; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{12}H_8N_3O_5I$, 409.9509; found, 409.9500.

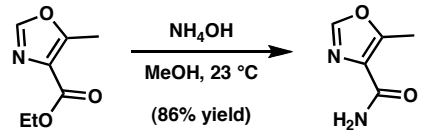



**Bisoxazole Iodo Triflate 226.** To bisoxazole triflate **214** (41.3 mg, 0.15 mmol) in THF (3.0 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 65 μL, 0.16 mmol) in a dropwise fashion. After stirring at –78 °C for 30 min, a separate solution of $I_2$ (43.9 mg, 0.17 mmol) in THF (1.0 mL) cooled to –78 °C was added via cannula. Additional THF (0.5 mL) was used to rinse the cannula, which was added to the reaction mixture. The reaction was stirred at –78 °C for 1.5 h, allowed to thaw to 23 °C, and concentrated in vacuo. The residue was purified directly by flash chromatography (3:1 hexanes:EtOAc eluent) to provide bisoxazole iodo triflate **226** (51.5 mg, 86% yield) as a yellow solid. Suitable crystals for X-ray diffraction were obtained by vapor diffusion of heptane into an EtOAc solution of **226** at 23 °C. $R_f$ 0.30 (4:1 hexanes:EtOAc); mp 96–98 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.74 (s, 1H), 7.75 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 152.0, 145.8, 145.1, 132.9, 127.1, 118.8 (q, $J_{CF}$ = 320 Hz), 103.4; $^{19}$F NMR (282 MHz,

$CDCl_3$) δ –73.2; IR (film) 3451 (br), 1585, 1430, 1221 $cm^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_2F_3IN_2O_5S$, 409.8681; found, 409.8693.

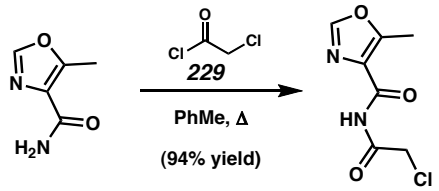



**Methyl Oxazole Ethyl Ester 227.**[35] To a solution of ethyl isocyanoacetate (**217**, 1.13 g, 10.0 mmol) in THF (12 mL) at 0 °C was added DBU (3.0 mL, 20.0 mmol), followed by dropwise addition of a solution of acetic anhydride (1.89 mL, 20.0 mmol) in THF (8 mL). The mixture was stirred at 0 °C for 30 min and then at 23 °C for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (3:2 hexanes:EtOAc eluent) to give methyl oxazole ethyl ester **227** (1.54 g, 90% yield) as a yellow oil. Characterization data for this compound have been reported previously.[35] $R_f$ 0.47 (1:1 hexanes:EtOAc); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 162.4, 156.6, 149.0, 127.5, 61.2, 14.5, 12.1; IR (film) 3129, 2983, 1716, 1615, 1105 $cm^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_9NO_3$, 155.0582; found, 155.0585.




*227* *228*

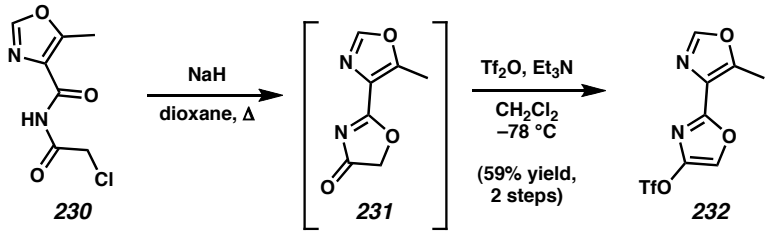
**Methyl Oxazole Amide 228.** To a solution of methyl oxazole ester **227** (1.55 g, 10 mmol) in MeOH (25 mL) was added concentrated ammonium hydroxide (28–30%, 25 mL) in one portion at 23 °C. The reaction mixture was stirred at 23 °C for 66 h, and then the solvent was evaporated under reduced pressure. The crude product was adsorbed onto silica gel using MeOH as solvent, and purified by flash chromatography (12:1 $CHCl_3$:MeOH eluent) to yield methyl oxazole amide **228** (1.07 g, 86% yield) as a white solid. $R_f$ 0.41 (10:1 $CHCl_3$:MeOH); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.29 (s, 1H), 7.48 (br s, 1H), 7.40 (br s, 1H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 163.1, 152.4, 149.4, 128.6, 11.2; IR (KBr) 3391, 3154, 1690, 1621, 1193, 1121 cm$^{-1}$; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_5H_6N_2O_2$, 126.0429; found, 126.0435.




*228* *230*

**Methyl Oxazole Chloro Imide 230.** To methyl oxazole amide **228** (732.6 mg, 5.81 mmol) in toluene (6 mL) was added chloroacetyl chloride (**229**, 650 μL, 8.17 mmol) over 30 sec at 23 °C. The flask was fitted with reflux condenser and a drying tube containing Drierite®, and the reaction mixture was heated at 115 °C for 9 h under gentle reflux. The reaction was allowed to cool to 23 °C, and hexanes (50 mL) was added. The suspension was vigorously stirred for 2 h at 23 °C. The product was collected by vacuum

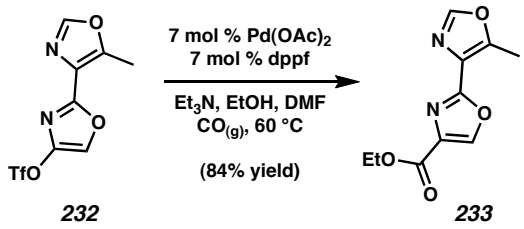
filtration, rinsed with hexanes (3 x 10 mL), and further dried under high vac to afford methyl oxazole chloro imide **230** (1.10 g, 94% yield) as a white solid. $R_f$ 0.50 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.64 (br s, 1H), 8.48 (s, 1H), 4.70 (s, 2H), 2.61 (s, 3H); $^{13}$C NMR (300 MHz, DMSO-$d_6$) δ 166.8, 159.9, 156.3, 150.0, 127.3, 45.0, 11.5; IR (film) 3261, 1732, 1724, 1704, 1614, 1482, 1180 cm$^{-1}$; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_7H_7N_2O_3Cl$, 202.0145; found, 202.0142.




**Methyl Bisoxazole Triflate 232.** To a well-stirred suspension of NaH (60% dispersion in mineral oil, 251.2 mg, 6.28 mmol) in dioxane (90 mL) was slowly added chloro imide **230** (1.096 g, 5.41 mmol) over 1 min at 23 °C. After stirring 15 min at this temperature, the reaction was heated at 110 °C for 40 min and then allowed to cool at 23 °C for 20 min, and then at 10 °C for 30 min. The mixture was filtered over a pad of Celite® ($Et_2O$ eluent), and then evaporated in vacuo, coevaporating with heptane (3 x 100 mL) and benzene (50 mL). Trace volatiles were removed by high vac to afford oxazolone **231**, which was immediately used in the subsequent reaction.

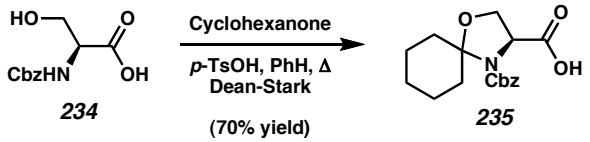
To a solution of oxazolone **231** in $CH_2Cl_2$ (30 mL) at –78 °C was added $Et_3N$ (1.5 mL, 10.8 mmol) dropwise over 1 min. Freshly prepared $Tf_2O$ (1.1 mL, 6.5 mmol) was then added dropwise over 2 min. After stirring for 45 min at –78 °C, the reaction was immersed in a 0 °C bath for 15 min. The reaction was quenched at 0 °C by the addition of $H_2O$ (100 mL), and the phases were partitioned. The aqueous phase was further extracted

with $CH_2Cl_2$ (3 x 100 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to afford methyl bisoxazole triflate **232** (955.6 mg, 59% yield, 2 steps) as an orange solid. $R_f$ 0.19 (4:1 hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.73 (s, 1H), 2.68 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 154.0, 152.2, 150.3, 145.9, 126.3, 124.4, 118.8 (q, $J_{CF}$ = 321 Hz), 11.7; $^{19}$F NMR (282 MHz, $CDCl_3$) δ –73.2; IR (film) 3133, 1647, 1589, 1435, 1229, 1137 cm$^{-1}$; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_8H_5N_2O_5F_3S$, 297.9871; found, 297.9862.



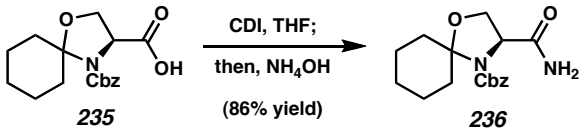

**Methyl Bisoxazole Ethyl Ester 233.** Methyl bisoxazole triflate **232** (1.46 g, 4.90 mmol), $Pd(OAc)_2$ (77.2 mg, 0.34 mmol), 1,1'-bis(diphenylphosphino)ferrocene (190.9 mg, 0.34 mmol), and DMF (27 mL) were combined in a 250 mL sealable Schlenk flask. EtOH (5.8 mL, 99.3 mmol) and $Et_3N$ (1.9 mL, 13.6 mmol) were rapidly added, and the solution was sparged with carbon monoxide gas for 15 min. The flask was sealed and heated at 60 °C for 12 h. The solution was allowed to cool to 23 °C, and was sparged with argon for 15 min *(Caution: CO gas!)*. EtOAc (300 mL) and $H_2O$ (100 mL) were added, and the phases were separated. The aqueous layer was further extracted with EtOAc (2 x 200 mL). The combined organics were washed with 0.1 M HCl (50 mL), $H_2O$ (50 mL), and brine (50 mL), dried over $MgSO_4$, and evaporated in vacuo. Purification by flash chromatography (7:1 $CH_2Cl_2$:EtOAc eluent) furnished methyl

bisoxazole ethyl ester **233** (913.5 mg, 84% yield) as a brown-tan solid. $R_f$ 0.35 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.82 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.74 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.3, 156.7, 151.7, 149.9, 143.5, 134.7, 124.5, 61.5, 14.5, 11.9; IR (film) 3127, 2983, 1739, 1720, 1576, 1316, 1113 cm$^{-1}$; HRMS-EI (*m/z*): [M]$^+$ calc'd for $C_{10}H_{10}N_2O_4$, 222.0641; found, 222.0648.

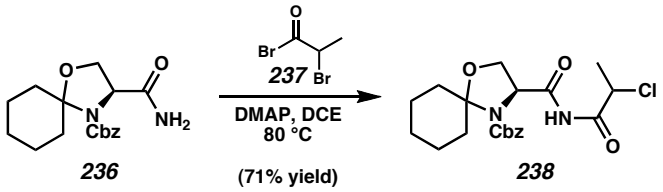



**Acid 235.** To *N*-Cbz-serine[36] (**234**, 5.0 g, 20.9 mmol) in benzene (150 mL) was added cyclohexanone (3.0 mL, 28.9 mmol) and *p*-toluenesulfonic acid (420 mg, 2.2 mmol). The mixture was heated to reflux under a Dean-Stark trap for 18 h and then was allowed to cool to 23 °C. The reaction mixture was poured over saturated aq. $NaHCO_3$ (100 mL), and the phases were partitioned. The aqueous phase was further extracted with $Et_2O$ (2 x 100 mL), and the combined organics were extracted with saturated aq. $NaHCO_3$ (2 x 100 mL). The aqueous phases were all combined, acidified to pH = 2 using 3 M HCl, and extracted with EtOAc (2 x 150 mL). The combined EtOAc extracts were washed with 1 N HCl (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo to provide acid **235** (4.64 g, 70% yield) as an off-white foam. $R_f$ 0.24 (1:1 hexanes:EtOAc; 1% acetic acid); $^1$H NMR (500 MHz, $C_6D_6$, 70 °C, mixture of rotamers) δ 7.24–7.03 (comp. m, 5H), 5.09 (d, *J* = 12.7 Hz, 1H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.31–4.24 (m, 1H), 3.95–3.80 (m, 1H), 3.65–3.58 (m, 1H), 2.83–1.00 (comp. m, 10H); $^{13}$C NMR (125 MHz, $CDCl_3$, major rotamer) δ 177.0, 152.0, 136.5, 128.7 (2C), 128.2,

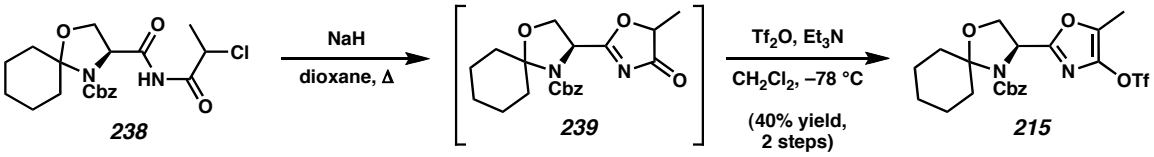
127.9 (2C), 97.2, 67.1, 66.6, 58.8, 33.5, 31.6, 24.8, 23.5, 23.4; IR (film) 2935 (br), 1713 (br), 1415, 1351, 1211, 1085 $cm^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{17}H_{21}O_5N$, 319.1240; found, 319.1435; $[\alpha]^{20}_D$ –26.99° (*c* 1.0, MeOH).




**Amide 236.** To acid **235** (6.12 g, 19.2 mmol) in THF (80 mL) at 23 °C was added 1,1'-carbonyldiimidazole (6.15 g, 37.9 mmol) in one portion. The reaction was stirred for 15 min, then concentrated ammonium hydroxide (28.0–30.0% in $H_2O$, 20 mL) was added in a steady stream. After 3 h of additional stirring at 23 °C, the reaction mixture was poured over EtOAc (200 mL) and 10% aq. citric acid (100 mL). The phases were partitioned, and the organic extract was washed with 1 M HCl (5 x 50 mL) until the pH of the aqueous phase was less than 2. The organic phase was further washed with saturated aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to yield amide **236** (5.24 g, 86% yield) as a white foam. $R_f$ 0.42 (3:1 EtOAc:hexanes); $^1$H NMR (500 MHz, $CDCl_3$, 50 °C, mixture of rotamers) δ 7.37–7.27 (comp. m, 5H), 6.02 (br s, 1H), 5.31 (br s, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 4.40 (app. d, *J* = 6.6 Hz, 1H), 4.31–4.20 (m, 1H), 2.05 (app. t, *J* = 7.9 Hz), 2.51–2.33 (m, 1H), 2.24–2.11 (m, 1H), 1.72–1.45 (comp. m, 7H), 1.28–1.10 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 173.8 (br), 136.1, 128.8 (2C), 128.5, 128.1 (2C), 97.1, 67.4 (br), 67.2 (br), 60.4, 35.4 (br), 29.9 (br), 24.8, 23.5, 23.3; IR (film) 3335, 3197, 2934, 1694 (br), 1410, 1349, 1084 $cm^{-1}$; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{17}H_{22}N_2O_4$, 319.1580; found, 318.1584; $[\alpha]^{19}_D$ –19.56° (*c* 0.5, MeOH).




**Chloroimide 238.** To amide **236** (0.80 g, 2.51 mmol) in 1,2-dichloroethane (17 mL) at 23 °C was added DMAP (590.9 mg, 4.84 mmol), followed by dropwise addition of 2-bromopropionyl bromide (**237**, 470 μL, 4.49 mmol). The solution was heated at 80 °C for 3 h and was then allowed to cool to 23 °C. The reaction mixture was purified directly by flash chromatography (7:1 hexanes:EtOAc → 4:1 hexanes:EtOAc eluent) to afford chloroimide **238** (0.73 g, 71% yield) as a colorless oil. $R_f$ 0.20 (4:1 hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$, 50 °C, mixture of rotamers) δ 8.86 (br s, 1H), 7.36–7.26 (comp. m, 5H), 5.20–5.05 (m, 2H), 4.92–4.87 (m, 1H), 4.61–4.47 (m, 1H), 4.24–4.08 (comp. m, 2H), 2.55–1.10 (comp. m, 13H); $^{13}$C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 171.0 (br), 169.2, 136.1, 128.8 (2C), 128.4, 128.1, 128.0, 97.4 (br), 67.4 (br), 61.5 (br), 54.9, 54.7, 34.3 (br), 31.0 (br), 24.8, 23.5, 21.6, 21.5; IR (film) 3275, 3208, 2936, 1743, 1715, 1413, 1348, 1204 cm$^{-1}$; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{20}H_{26}N_2ClO_5$, 409.1530; found, 409.1525; $[\alpha]^{20}_D$ –44.89° (*c* 1.0, MeOH).




**Methyl Oxazole Triflate 215.** To a slurry of NaH (60% dispersion in mineral oil, 105.9 mg, 2.65 mmol) in dioxane (24 mL) at 23 °C was added a solution of chloroimide **238** (1.00 g, 2.45 mmol) in dioxane (13 mL) in a steady stream. Immediately after the

addition, the flask was fitted with a reflux condenser and was heated at 110 °C for 1 h. The flask was then allowed to cool to 23 °C over 2 h and was filtered over a pad of Celite® ($CH_2Cl_2$ eluent). The filtrate was concentrated to a viscous, colorless oil. Benzene (10 mL) was added, and the volatiles were further evaporated in vacuo to afford oxazolone **239** as a white foam. This crude material was immediately carried to the subsequent step without further purification.

Crude oxazolone **239** was dissolved in $CH_2Cl_2$ (14 mL), and the resulting colorless solution was cooled to –78 °C. $Et_3N$ (615 μL, 4.41 mmol) was added, followed by dropwise addition of $Tf_2O$ (445 μL, 2.65 mmol). The solution was maintained at –78 °C for 2.5 h, quenched by addition of $H_2O$ (1 mL), and allowed to thaw to 23 °C. Additional $H_2O$ (10 mL) was added, and the phases were separated. The aqueous layer was further extracted with $CH_2Cl_2$ (5 x 5 mL), and the combined organics were dried over $MgSO_4$, and concentrated to a brown oil. Purification of the crude product by flash chromatography (19:1 hexanes:EtOAc eluent) gave methyl oxazole triflate **215** (499.1 mg, 40% yield, 2 steps) as a white solid. $R_f$ 0.37 (4:1 hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.40–7.12 (comp. m, 5H), 5.20–4.90 (comp. m, 3H), 4.19–4.05 (comp. m, 2H), 2.49–1.04 (comp. m, 10H), 2.19 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, major rotamer) δ 158.8, 151.9, 140.6, 138.1, 136.3, 128.6 (2C), 128.3, 128.1 (2C), 118.7 (q, $J_{CF}$ = 321 Hz), 97.2, 67.7, 67.1, 55.1, 33.7, 31.4, 24.7, 23.5, 23.5, 9.5; $^{19}$F NMR (282 MHz, $CDCl_3$) δ –73.5; IR (film) 2937, 1715, 1430, 1348, 1226, 1135 cm$^{-1}$; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{21}H_{24}SN_2O_7F_3$, 505.1256; found, 505.1232; $[\alpha]^{20}_D$ –1.03° (*c* 1.0, MeOH).

**4.5 Notes and References**

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(2) Reprinted, with permission, from: Shay, J. W.; Wright, W. E. *Nat. Rev. Drug Discovery* **2006**, *5*, 577–584 (Copyright 2006 Macmillan Publishers Ltd).

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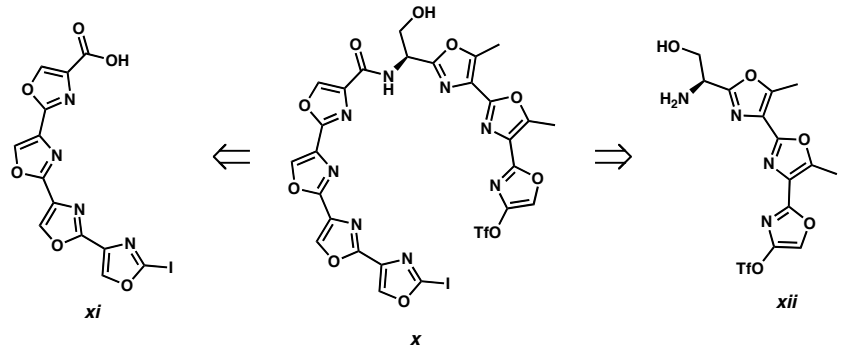


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(28) Although no characterization data or experimental details were provided, the synthesis of compound **214** via a related route was recently reported. See reference 20d.

(29) (a) See Section 4.4 Experimental Section. (b) Iodobisoxazole triflate **226** is shown with 50% probability ellipsoids (Note: Only *Molecule A* is depicted). 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 282586.

(30) For useful reports of oxazole cross-couplings, see references 20b–d and references therein.

(31) For Negishi cross-couplings of oxazoles, see: (a) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453–9456. (b) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583–585. (c) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634–8639. (d) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011–1014. (e) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, H. R.; Pangborn, J. *J. Org. Process Res. Dev.* **2003**, *7*, 696–699.

(32) Although no characterization data or experimental details were provided, the syntheses of compounds **224** and **225** were recently reported. See reference 20d.

(33) Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299–301.

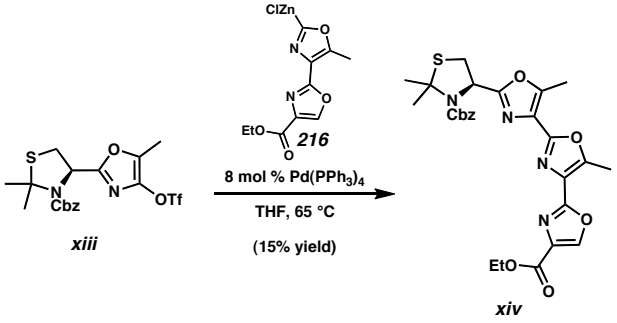
(34) It was found that dichloromethane added sufficient solubility to aid with deprotonation.

(35) Tormyshev, V. M.; Mikhalina, T. V.; Rogozhnikova, O. Y.; Troitskaya, T. Y.; Trukhin, D. V. *Russ. J. Org. Chem.* **2006**, *42*, 1049–1053.

(36) (a) Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536–1547. (b) Hwang, D.-R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264–1271. (c) Scheurer, A.; Mosset, P.; Bauer, W.; Saalfrank, R. W. *Eur. J. Org. Chem.* **2001**, 3067–3074.

(37) The acetonide protecting group was initially employed instead of a cyclohexylidene moiety, but it was found to be labile in later steps.

(38) Cross-coupling attempts using oxazole triflate **215** and a suitable trisoxazole partner to form tetrakisoxazole triflate **243** directly were not explored, due to the near certainty of competition between the various oxazole triflates. Cross-couplings in a related system to form ester **xiv** were met with limited success.



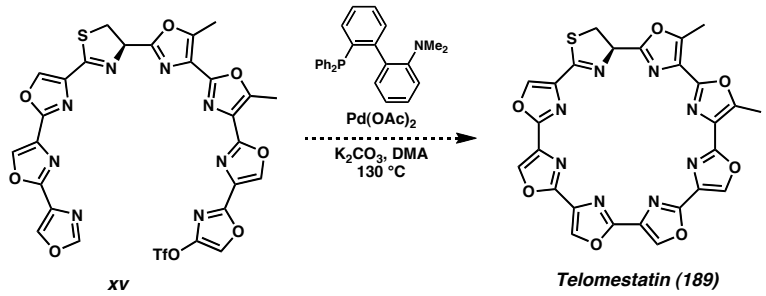

(39) Preliminary experiments have resulted in the preparation of milligram quantities of tetrakisoxazole triflate **243** using the described route.

(40) Altenbach, H.-J.; Himmeldirk, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1077–1080.

(41) (a) Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C.; Roberts, E. *J. Med. Chem.* **1992**, *35*, 1472–1484. (b) Pontillo, J.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1407–1411.

(42) Metal ions are known to promote intramolecular macrocyclizations via a templating effect, and may be useful for the final step. See: (a) Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 2780–2782. (b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469–475. (c) Blake, A. J.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G. *Synlett* **2000**, 1515–1518 and references therein. For a recent report, see: (d) Xu, Y.; Chen, L.; Ma, Y.; Li, J.; Cao, X. *Synlett* **2007**, 1901–1904 and references therein.

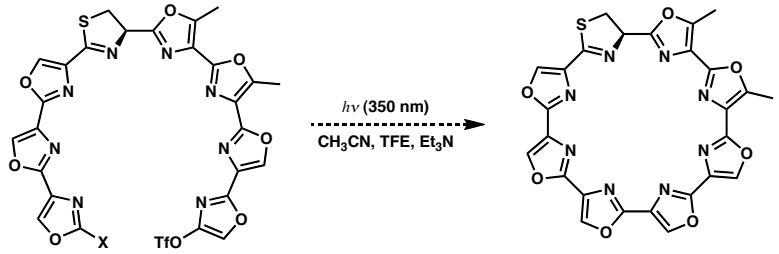
(43) An alternate macrocyclization strategy via direct arylation may also be possible (i.e., **xv** → **189**). For pertinent references, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187. (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590. (d) Miki, Y.; Shirokoshi, H.; Asai, M.; Aoki, Y.; Matsukida, H. *Heterocycles* **2003**, *60*, 2095–2101.




*xv* *Telomestatin (189)*

(44) A final macrocyclization approach involving a Witkop photocyclization would be promising option as well (i.e., **244** or **xv** → **189**). For relevant examples, see: (a) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713–721. (b) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961–4966. (c) De Carolis, M.; Protti, S.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1232–1236. (d) Freccero, M.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2003**, *125*, 13182–13190. (e) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2005**, *7*, 5449–5452. (f) Mangion, I. K. "Development of Organocatalytic Direct Aldol Transformations, Total Syntheses of Brasoside and Littoralisone, and Progress Toward the Total

Synthesis of Diazonamide A." Ph.D. Thesis, California Institute of Technology, 2006. http://resolver.caltech.edu/CaltechETD:etd-05232006-210214




***xv,*** **X = H**
***244,*** **X = I**

***Telomestatin (189)***