New Methods for the α-Functionalization of Thioesters and Activated Hydrazones and an Application Toward the Total Synthesis of Apratoxin D

by

Emily Tarsis

Department of Chemistry
Duke University

Date:_____
Approved:

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Don M. Coltart, Supervisor

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Steven W. Baldwin

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Stephen L. Craig

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Michael C. Fitzgerald

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School
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ABSTRACT

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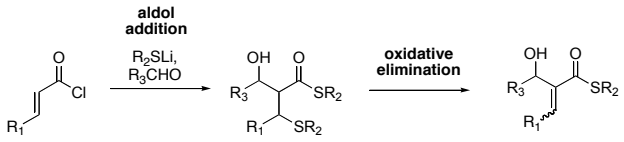
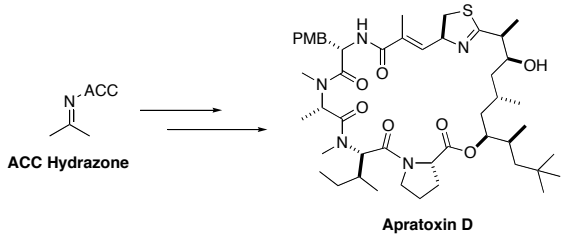
Abstract

Cascade reactions, also referred to as domino reactions, have been widely used for the formation of carbon–carbon bonds. This type of reaction has the potential to circumvent protection and deprotection steps, shortening an overall synthetic process. The Morita-Baylis-Hillman (MBH) reaction is a particularly notable example of an anionic domino reaction which provides straightforward access to β′-hydroxy-α,β-unsaturated carbonyl compounds from aldehydes and α,β-unsaturated carbonyls. However, despite the importance of the Baylis-Hillman reaction, it is slow, reaction yields are quite low, and the process is not general, as it rarely works for β-substituted α,β-unsaturated carbonyl species. Herein, we report an alternative approach to the preparation of MBH adducts employing an *anti*-selective direct aldol cascade reaction followed by oxidative elimination. This alternative process is rapid, efficient, and generally applicable, even to β-substituted α,β-unsaturated compounds.



Progress toward the asymmetric total synthesis of apratoxin D is described. The key step of the synthesis is the asymmetric α,α-bisalkylation of chiral *N*-amino cyclic carbamate (ACC) hydrazones, a new methodology developed by our group. Herein we demonstrate the utility of this method for convergent total syntheses.



Dedicated to the memory of George Michael Tarsis, Jr.

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Acknowledgements

First, and most importantly, I want to extend my deepest thanks to my advisor, Professor Don Coltart for his support, encouragement, and patience throughout my graduate career. Don provided me with the opportunity to join his research group although I had no prior experience in synthetic organic chemistry. Don has continued to push me to become a better chemist, and I am truly grateful to have had the opportunity to work with him.

I would also like to thank the members of my dissertation committee, Professor Steven Baldwin, Professor Stephen Craig, and Professor Michael Fitzgerald for taking the time to read my dissertation and offer suggestions. In particular, I am grateful to Dr. Baldwin for his letter of recommendation for my postdoctoral position.

I'm also grateful to the other past and present members of the Coltart lab for their friendship, support, and collaborations. Our lab has been an inspiring work environment because of the motivation that you guys provided through conversations about research.

Finally, I want to thank my Family for their love and support throughout my entire academic career. In particular, I thank my fiancée Graham for his patience and support during a very difficult time, without which I would not have been able to finish my graduate studies.

1. A Rapid and General Synthesis of α-Alkenyl-β'-hydroxy Thioesters

1.1 Background and Introduction

1.1.1 Carbon-Carbon Bond Formation

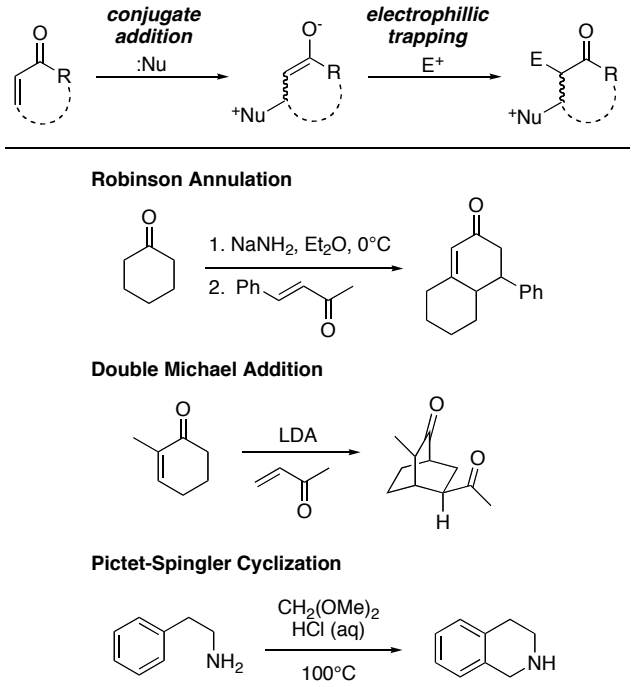
Reactions that form carbon–carbon bonds comprise the most important general class of transformations in synthetic organic chemistry. The reaction between a nucleophilic carbon in the form of an enolate and an electrophilic carbon is one of the most important methods for carbon–carbon bond formation, and has provided the foundation for the advancement of synthetic organic chemistry to its present state. Of particular importance is the aldol addition reaction. This reaction is one of the most widely used methods for the construction of polyketide natural products providing access to complex classes of natural products, such as erythromycins and epothilones [1]. Remarkable advances have been made in the stereo-, regio-, and chemoselectivity of this process [2, 3]. Many of the methods that address these selectivity issues take advantage of carboxylate-derived, preformed enolates [2, 3]. While effective, the step-wise procedures necessary to generate such enolates are time consuming and require that all manipulations be conducted under anhydrous conditions and at low temperatures when strong bases are used. In an effort to develop milder and operationally-simplified methods for carbon–carbon bond formation, there has been increased interest in the *direct* aldol reaction [4-10].

Direct reactions are those that are conducted by simply combining appropriate substrates and reagents to form the desired product without additional manipulations, such as prior enolate formation. Given the highly complex nature of enolate-based transformations, to be of general use, a direct reaction must possess control elements to

ensure chemoselective enolate formation. In a base-mediated aldol reaction, chemoselectivity is a concern when the aldeyde acceptor has one or more α-protons, as it can enolize, in addition to the intended enolate donor (e.g., carboxylate derivative). This, of course, stems from the enhanced acidity of aldehydes in comparison to typical carboxylate derivatives, suggesting that a non-basic means of enolization would be highly beneficial. Overcoming the chemoselectivity issue is, thus, the first critical step toward developing a generally applicable direct aldol addition.

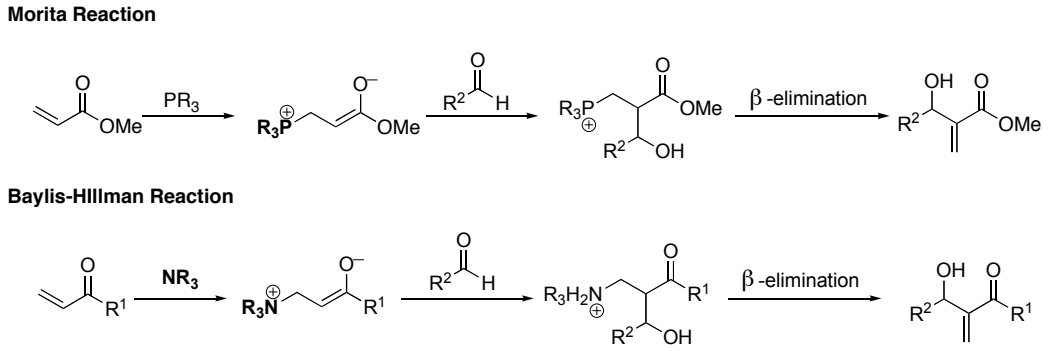
Cascade reactions, also referred to as domino reactions, have been widely used for the formation of carbon–carbon bonds [11]. This type of reaction forms at least two new bonds in a single chemical operation, and has the potential to circumvent protection and deprotection steps, shortening an overall synthetic process [12, 13]. Cascade reactions have been applied to the synthesis of several biologically active compounds, including steroids, prostaglandins, and terpenes [14].

The most commonly used domino process is the anionic domino reaction, which is usually initiated by the conjugate addition of a nucleophile to an enone. This process generates an enolate in situ that can then be trapped by an electrophile, such as another α,β-unsaturated carbonyl compound, an aldehyde, a ketone, an imine, an ester, or an alkyl halide (Scheme 1) [11]. Some typical examples include the Robinson annulation,[15, 16] double Michael reaction [14], Pictet-Spengler cyclization [17, 18], and the Morita-Baylis-Hillman reaction [19, 20].



Scheme 1. Anionic Domino Reactions Via In Situ Enolate Formation

The Morita-Baylis-Hillman (MBH) reaction is a particularly notable example of an anionic domino reaction, and has received considerable attention by synthetic chemists. This reaction provides straightforward access to β'-hydroxy-α,β-unsaturated carbonyl compounds from aldehydes and α,β-unsaturated carbonyls (Scheme 1) [19-21]. Morita reported the tertiary phosphine catalyzed reaction between various aldehydes and acrylonitrile or methyl acrylate in 1968 [20]. The related trasformation was performed four years later by A. B. Baylis and M. E. D. Hillman using the cheaper and less toxic catalyst, DABCO, a tertiary amine [19]. In addition, Baylis and Hillman reported the reaction in the context of a variety of conjugated carbonyl compounds, including esters, nitriles, amides and ketones.



Scheme 2. Morita-Baylis-Hillman Reaction

The mechanism of this reaction involves the conjugate addition of a tertiary amine (or phosphine) to form an enolate, followed by aldol addition and β-elimination. Given the highly functionalized nature of the products obtained, they are very useful synthetic intermediates and have been used in various ways in the total syntheses of a variety of natural products and other related compounds [21-26]. For example, D. Basavaiah and co-workers synthesized (*E*)-*p*-(myristyloxy)-α-methylcinnamic acid using a nucleophilic hydride addition to the Baylis-Hillman adduct [27]; J. Jauch applied this reaction to the synthesis of kuehneromycin A [28]; and E. J. Corey and coworkers applied an intramolecular Baylis-Hillman reaction in the total synthesis of salinosporamide A (Figure 1) [29].

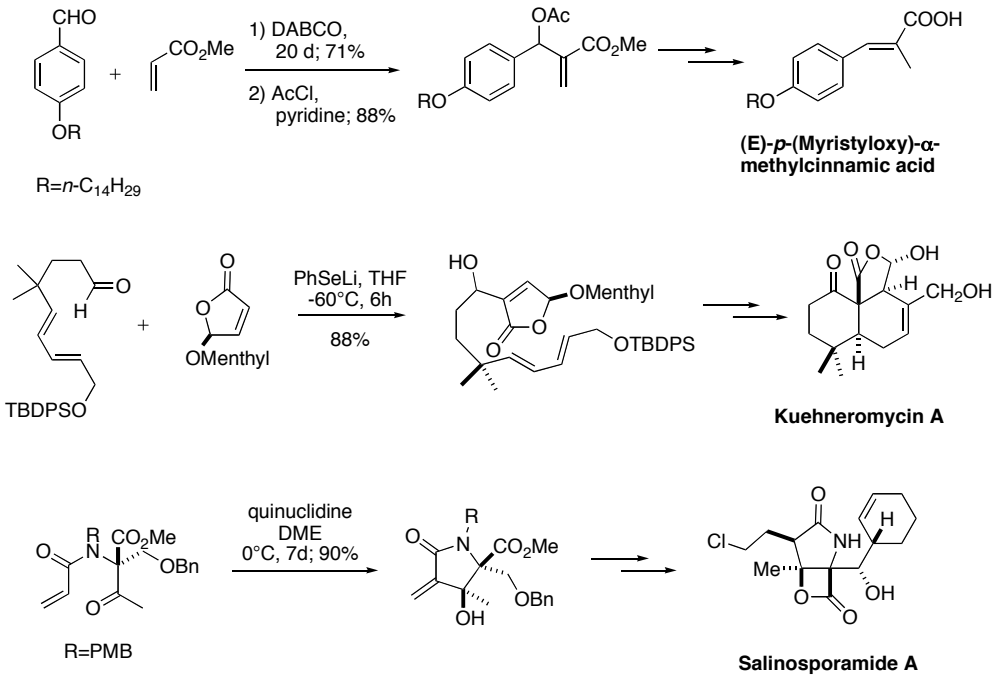
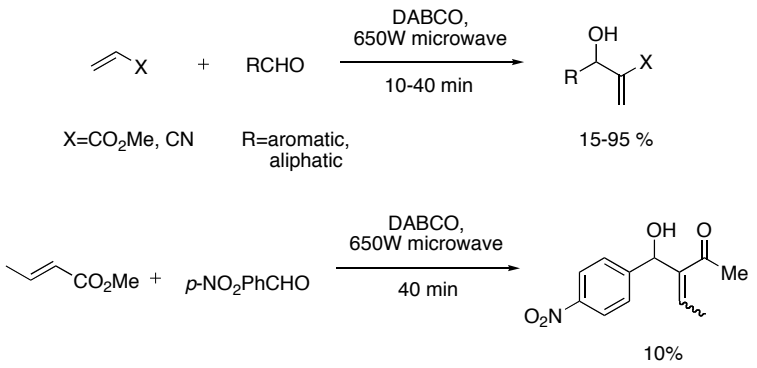


Figure 1. Natural Products Synthesized with Baylis-Hillman Reactions

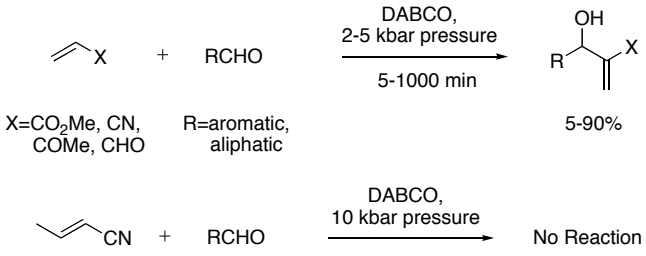
Despite the importance of the Baylis-Hillman reaction, it is remarkably slow, requiring up to weeks to complete [21]. Furthermore, reaction yields are often quite low, and the process is not general, as it rarely works for β-substituted α,β-unsaturated carbonyl species [21]. Recent modifications to the Baylis-Hillman reaction have been investigated in an attempt to overcome these shortcomings, including the addition of Lewis-acids[21], microwave irradiation [30], high pressure [31, 32], high temperature and ultrasound [33], and aqueous media [34], Kundu et. al. demonstrated significant rate enhancements for acrylate esters or acrylonitrile with both aliphatic and unsaturated aldehydes using microwave irradiation [30]. However, the yields remained variable and the only really high yielding reaction was with an activated aldehyde (4-

nitrobenzaldhyde). The use of microwaves also did not provide a general solution, as the attempt to carry out the reaction with a β-substituted (crotyl) substrate only reacted in 10 % yield (Scheme 3) [30].



Scheme 3. Microwave Mediated Baylis-Hillman Reaction

Hill and Isaacs reported increased reaction rate and improved yields in some cases using high pressure, but this method was only applicable to acrylate systems (Scheme 4) [31].



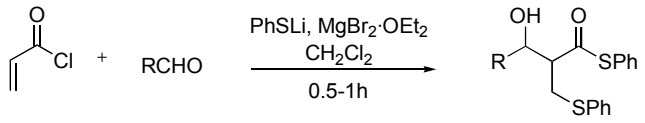
Scheme 4. Pressure Mediated Baylis-Hillman Reaction

Roos and Rampersadh reported increased reaction rates when ultrasound was applied with elevated temperatures, but they did not report the reaction yields, and, as with other modifications, the method was only applied to acrylate substrates [33]. While

some progress has been made toward an improved MBH reaction, reaction rates and yields remain highly variable, and none of these modifications has successfully addressed the lack of generality of the reaction by expanding the scope to include β-substituted α,β-unsaturated carbonyl species. Herein, we report an alternative approach to the preparation of MBH adducts that is rapid, efficient, and generally applicable, even to β-substituted α,β-unsaturated compounds.

1.1.2 Four-Component Direct Aldol Cascade Reaction

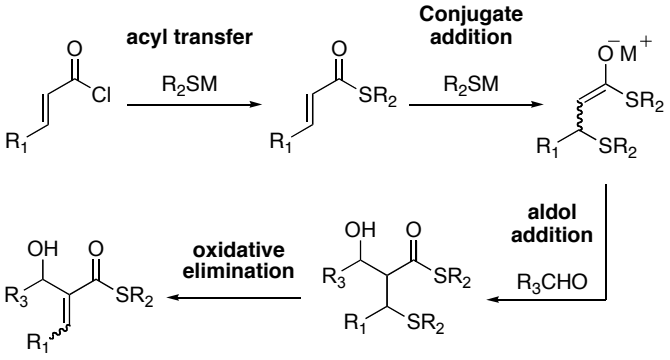
Our group recently reported an operationally simple $MgBr_2 \cdot OEt_2$-promoted four-component direct aldol addition between aldehydes and a thioester enolate, obtained by conjugate addition of lithium thiophenolate to an in situ-formed α,β-unsaturated thioester (Scheme 2) [35]. The efficiency of this reaction stems from the high nucleophilicity of thiolates in forming the requisite magnesium enolates, followed by the rapid addition of these enolates to aldehydes [36]. This reaction is compatible with a variety of aldehydes, including those that are enolizable, and can be conducted open to the air using untreated, reagent-grade solvents at room temperature [35].



Scheme 5. Four-Component Direct Aldol Addition

Given the pronounced nucleophilicity of thiolates, we reasoned that the scope of the coupling could be extended to α,β-unsaturated carbonyl species having β-substituents. If this indeed were the case, then we could potentially connect this feature with the straightforward and rapid oxidative elimination of thioethers [37-40], thereby

developing a two-step procedure that is formally equivalent to the MBH reaction (Scheme 6), yet potentially consistently high-yielding, rapid, and most notably, general in scope. While overall this approach would introduce the requirement of an oxidation step, the resulting decrease in the duration of the reaction and increase in scope would more than compensate for the additional step.



Scheme 6. Proposed Four-Component Direct Aldol Addition/Oxidative Elimination Sequence

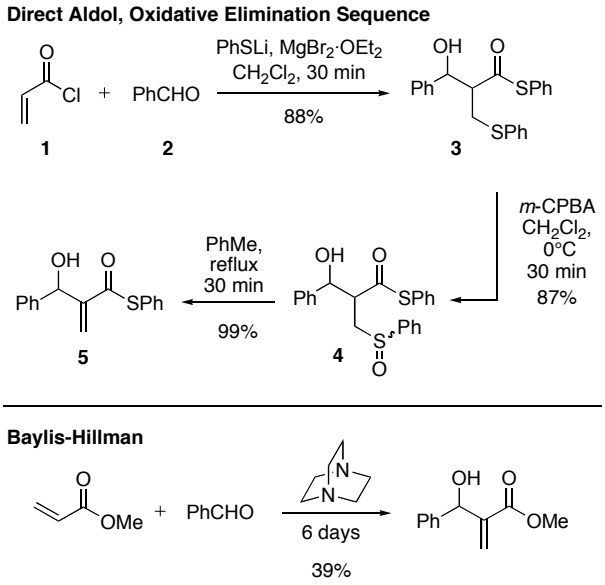
1.2 Two-step Sequence to β'-Hydroxy-α,β-unsaturated Carbonyl Compounds

1.2.1 Oxidative Elimination

In order to explore the thiolate-mediated oxidative MBH reaction, we first had to establish that we could carry out the oxidation chemoselectively. The aldol intermediates contain a free alcohol and possess divalent sulfur in the form of both a thioester and thioether. We first had to establish that the thioether function could selectively be oxidized in the presence of the thioester while also suppressing the retro-aldol. Selective oxidation was not expected to be overly problematic since the sulfur atom in the thioester is considerably less nucleophilic than that in the thioether.

Provided that the oxidation conditions were suitably mild, we felt that the retro-aldol reaction should be avoidable.

To determine if the thioether could indeed be oxidized without competing side reactions, compound **3** was prepared from acryloyl chloride, benzaldehyde and lithium thiophenolate using our previously established method (Scheme 7) [35]. Gratifyingly, when this compound was treated with *m*-CPBA, the desired mono-oxidation product **4** was obtained as a mixture of sulfoxide diastereomers, with neither overoxidation of the sulfoxide nor the retro-aldol reaction detected (Scheme 7). The corresponding sulfone was obtained from this reaction in 7% yield due to the use of a slight excess of *m*-CPBA. Compound **4** was then heated to reflux in toluene for 30 minutes, giving the desired elimination product (**5**) in excellent yield. Overall, the process required 1.5 hours of reaction time and gave a 69% yield. By comparison, the Baylis-Hillman reaction between methyl acrylate and benzaldehyde performed under common conditions using DABCO as the catalyst has been reported to give only 39% yield of the oxoester equivalent of **5** after 6 days [14].

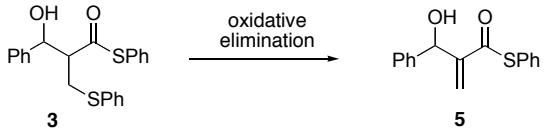


Scheme 7. Studies on the Stepwise Aldol Addition, Oxidation, and Elimination Sequence

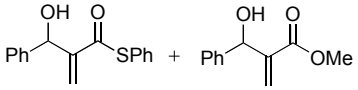
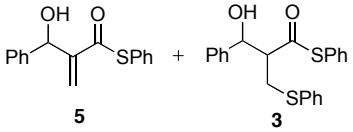
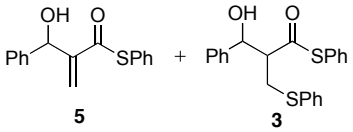
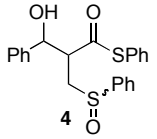
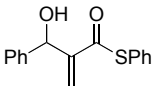
To simplify the overall process, we set out to develop a direct, one-pot protocol that would allow us to circumvent isolation and purification of the sulfoxide intermediate. To determine the best conditions for the oxidative-elimation sequence, we surveyed a variety of conditions using compound **3** as a model substrate (Table **1**). Initially we dismissed the use of *m*-CPBA, despite the success we had with it in our stepwise oxidative elimination procedure. *m*-CPBA is sold as an approximate weight percent, making it difficult to control the amount of oxidant used. In addition, the standard solvent used for *m*-CPBA oxidations is dichloromethane, which is relatively low boiling, so depending on whether the oxidation could be carried out in higher boiling solvents, this oxidant might not be amenable to a one-pot oxidative elimination protocol.

We started our survey of oxidative conditions with $NaIO_4$, one of the most widely used reagents for the selective oxidation of sulfides to sulfoxides [41]. However, use of $NaIO_4$ gave only modest yields of the desired elimination product in standard solvents (entries 1-3, Table 1), and when methanol was used a considerable amount of *S→O* acyl transfer product was obtained (entry 1). We then tried to promote the oxidative elimination using peroxymonosulfate (oxone), which is the potassium salt of peroxymonosulfuric acid (Caro's acid). Oxone is an attractive reagent because it is non-toxic, has a long shelf-life, is easy to handle, and has been used for oxidizing thioethers to either the sulfoxide or the sulfone, depending on the equivalents used [41]. Oxone proved to be an effective oxidant for the transformation, providing a very good yield of the desired product (entries 4 and 5). However, when we ran the oxidative elimination of some other substrates, they yields were lower and we observed formation of some of the sulfone. This prompted us to try *m*-CPBA in our one-pot protocol. We found that we could run this oxidation in toluene, and we found a reliable titration method for determining the exact weight percent. When we attempted the oxidative elimination with *m*-CPBA (entries 6 and 7), it gave even better yields than oxone, and we did not observe any overoxidation to the sulfone. With reliable one-pot oxidative elimination conditions, we shifted our focus to the aldol addition.

Table 1. Studies on the Oxidative Elimination of 3 to 5



3 **5**

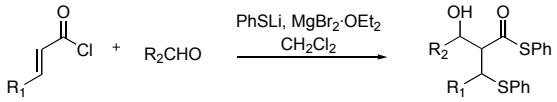
entry	conditions	time (h)	product(s) formed	ratio	isolated yield of **5** (%)
1	$NaIO_4$ (1.5 equiv), MeOH-H_2O (4:1), reflux	12	 **5** + **6**	2:1	46
2	$NaIO_4$ (1.5 equiv), THF-H_2O (4:1), reflux	12	 **5** + **3**	1:4.5	16
3	$NaIO_4$ (1.5 equiv), MeCN-H_2O (4:1), reflux	12	 **5** + **3**	9:1	39
4	Oxone (0.56 equiv), DMF-H_2O (1:1)	18	 **4**	n.a	n.a.
5	Oxone (0.56 equiv), DMF-H_2O (1:1), reflux	0.5	 **5**	n.a.	78
6	*m*-CPBA (1.0 equiv), CH_2Cl_2; then PhMe, reflux	0.5	**5**	n.a.	93
7	*m*-CPBA (1.0 equiv), PhMe, 0 °C to reflux	0.5	**5**	n.a.	96

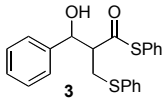
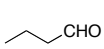
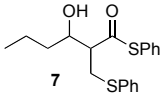
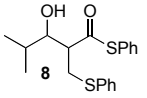
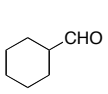
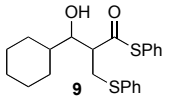
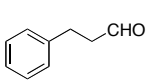
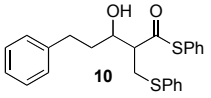
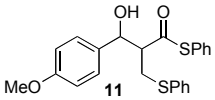
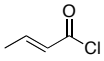
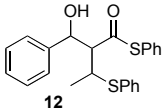
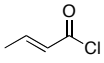
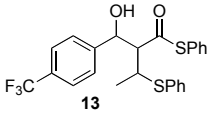
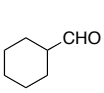
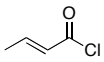
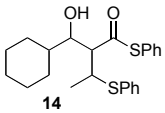
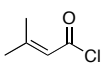
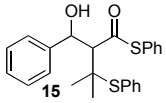
1.2.2 Scope of Aldol Addition

Having developed effective conditions for the oxidative-elimination sequence, we examined the scope of the four-component aldol addition reaction further. This was

done using a variety of aldehydes and α,β-unsaturated acid chlorides (Table 2), in addition to those that we had examined previously (entries 1-5) [35]. The four-component direct aldol addition proved very general and provided the desired products in a reasonably short period of time (30 min to 2h), with both electron rich and electron poor aldehydes. Hindered α-disubstituted aldehydes were also amenable to the cascade sequence and gave very good product yields (entries 3 and 4). Notably, as we had hoped, the thiolate-promoted aldol addition reaction proceeded effectively even the case of the β-substituted α,β-unsaturated acid chloride, crotonoyl chloride (entries 7-9). An especially interesting example appears in entry 9 where a hindered α-disubstituted aldehyde and a β-substituted α,β-unsaturated acid chloride gave the desired aldol product in good yield. The success of the aldol addition in these hindered systems prompted us to examine the β-disubstituted system, 3-methylbutenoyl chloride (entry 10), but even after 20 hours, only trace product (<5%) was observed.

Table 2. Four-Component Direct Aldol Addition Reaction

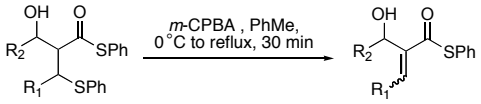


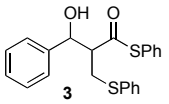
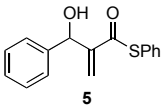
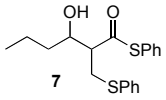
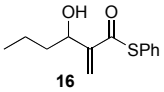
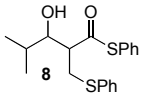
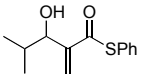
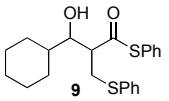
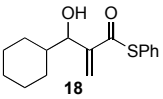
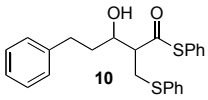
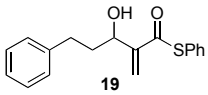
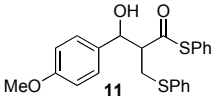
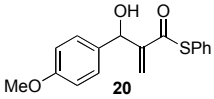
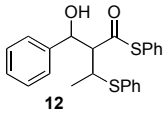
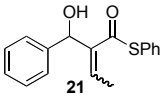
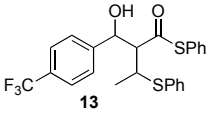
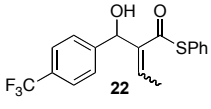
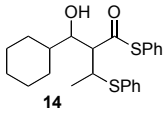
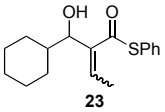
Entry	aldehyde	acid chloride	aldol Product	time (h)	yield (%)
1	PhCHO		 **3**	0.5	88
2			 **7**	0.5	71
3			 **8**	0.5	76
4			 **9**	0.5	81
5			 **10**	0.5	71
6	p-(OMe)PhCHO		 **11**	2.0	80
7	PhCHO		 **12**	2.0	68
8	p-(CF_3)PhCHO		 **13**	2.0	86
9			 **14**	1.0	61
10	PhCHO		 **15**	4.0	no reaction

1.2.3 Results of the Oxidative Elimination Step

Lastly we undertook the conversion of the aldol addition products into the corresponding α-alkenyl-β'-hydroxy thioesters using the oxidative-elimination protocol developed above. We were pleased to find that this transformation also proved both general and reliable (Table 3). In all cases, the elimination products were produced in very good to excellent yield, within only 30 minutes. Entries 7-9 are especially noteworthy as the products obtained equate to MBH couplings that would be extremely difficult, if not impossible, to achieve under conventional conditions.

Table 3. Oxidative Elimination Step



Entry	aldol Product	elimination product	E:Z	yield(%)
1	 **3**	 **5**	n.a.	96
2	 **7**	 **16**	n.a.	77
3	 **8**	 **17**	n.a.	84
4	 **9**	 **18**	n.a.	81
5	 **10**	 **19**	n.a.	88
6	 **11**	 **20**	n.a.	99
7	 **12**	 **21**	1:2,3	96
8	 **13**	 **22**	1:2.3	94
9	 **14**	 **23**	1:2.2	88

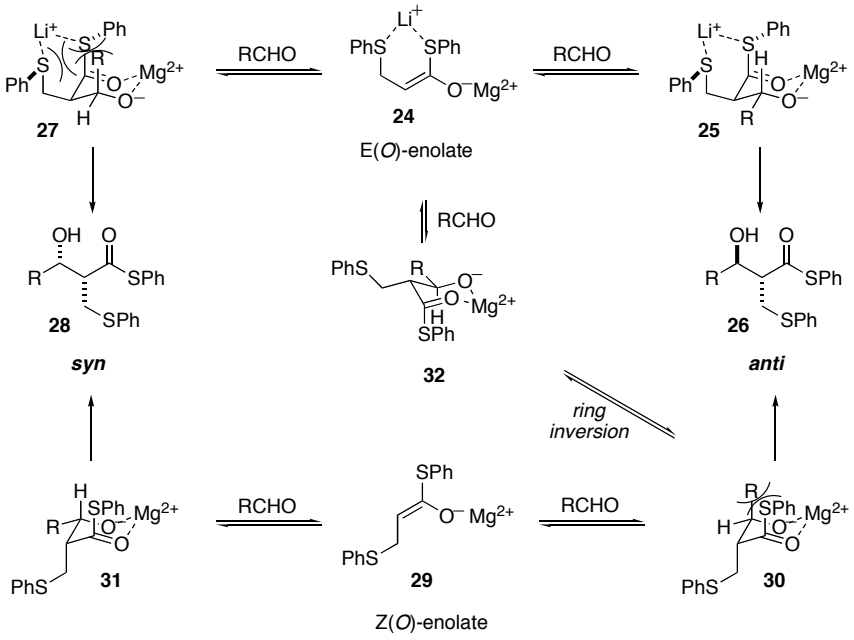
1.2.4 Analysis of the Diastereoselectivity

Assuming standard models [2, 3], the *anti*-selectivity of the aldol reaction of acryloyl chloride could originate from either kinetic addition of the E-(*O*)-enolate to the aldehyde, or from the relative thermodynamic stability of the *anti* and *syn* products. To determine whether the reaction was reversible, PhSLi was added to a mixture of $MgBr_2 \cdot OEt_2$, acryloyl chloride and PhCHO. After the reaction was complete, 4-methylbenzaldehyde was added and the reaction was continued for 15 min. This resulted in an approximately 1:1 mixture of addition products, each with a 13:1 *anti*-*syn* ratio, suggesting that the diastereoselectivity is thermodynamically controlled [35].

When the reaction was run with PhSNa instead of the PhSLi, longer reaction time was required and modest or no *anti*-selectivity was observed. This result suggests that Li^+ might not play a passive role in this transformation, and may in fact be strongly involved with generating the *anti*-selective aldol product. To test whether this was the case, the aldol addition was attempted with cyclohexane carboxaldehdye, acryloyl chloride and $MgBr_2 \cdot OEt_2$, using PhSMgBr in place of PhSLi. This reaction gave the corresponding aldol addition product with a 2:1 preference for the *syn* product, suggesting that Li^+ is a necessary component to achieving *anti*-selectivity. To confirm the importance of PhSLi, the reaction using PhSMgBr was repeated, adding PhSLi after 30 minutes. After 15 minutes, the ratio of aldol addition products was restored to >20:1 in favor of the *anti* product. Collectively, these results indicate that the stereochemical outcome of the reaction is strongly tied to the nature of the thiolate counter ion.

The model developed to rationalize this outcome as well as the reversible nature of the reaction proposes that, in the presence of Li^+, coordination with sulfur [42] leads

to the E-(*O*)-enolate (**24**), which reacts via the lower energy Zimmerman-Traxler transition state to give aldolate intermediate **25** preferentially over **27**, thus providing the *anti* product (Scheme 8). In the absence of Li^+, both the E-(*O*)-enolate (**24** minus Li^+) and the Z-(*O*)-enolate (**29**) exist, allowing *syn* product **28** to form via **31**, in addition to **26**. However, when PhSLi is added to the latter system prior to work up, *syn* intermediate **31** is converted to Li^+-complexed E-(*O*)-enolate (**24**) via a thermodynamically driven conformational ring inversion of **30** to **32**. Addition from **24** then gives *anti* product **26**, analogously to the first reaction containing only PhSLi.



Scheme 8. Stereochemical Model of the Aldol Addition with Acryloyl Chloride

When the aldol addition reaction is carried out with the β-substituted α,β-unsaturated acid chloride, crotonoyl chloride, an additional stereocenter is introduced, adding another level of complexity to the stereochemical analysis. The implication of

this additional stereocenter is that four diastereomers (and their enantiomers) could, in principle, be produced (four sets of diastereomers). However, only two diastereomers were detected, and they were produced in a ratio of approximately 2:1. This ratio is maintained in the products of the oxidative elimination, since they are formed in a stereospecific manner via a concerted syn-elimination (see below). We rationalized that Li^+ coordination with sulfur was still promoting formation of the E-(*O*)-enolate, as the additional bulk at the β-position of the acid chloride would actually disfavor formation of the Z-(*O*)-enolate due to increased $A^{1,3}$ strain in comparison to the acrylate-derived enolate (Figure 2).

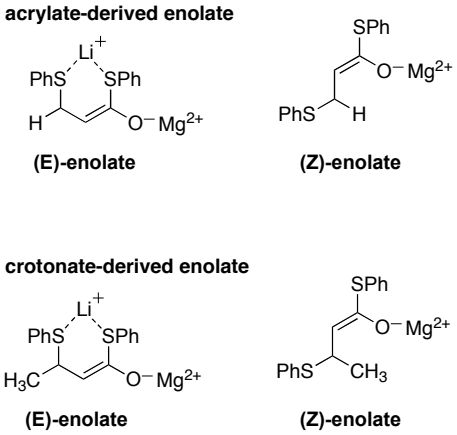
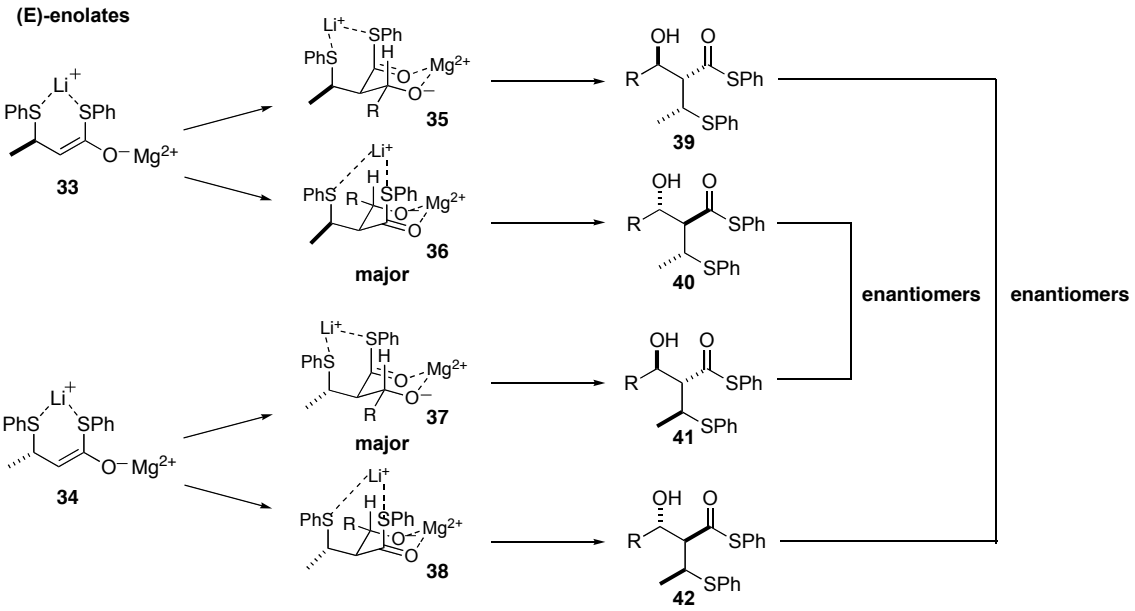


Figure 2. (E)-enolate vs. (Z)-enolate

Based on our previous determination that the reaction is under thermodynamic control, we can assume that the aldolates will form that minimize 1,3-diaxial interactions. With these assumptions in place, we were left with two possible E-(*O*)-enolates to analyze, formed from addition of the thiolate to either the top or bottom face of the α,β-unsaturated acid chloride (Scheme 9).

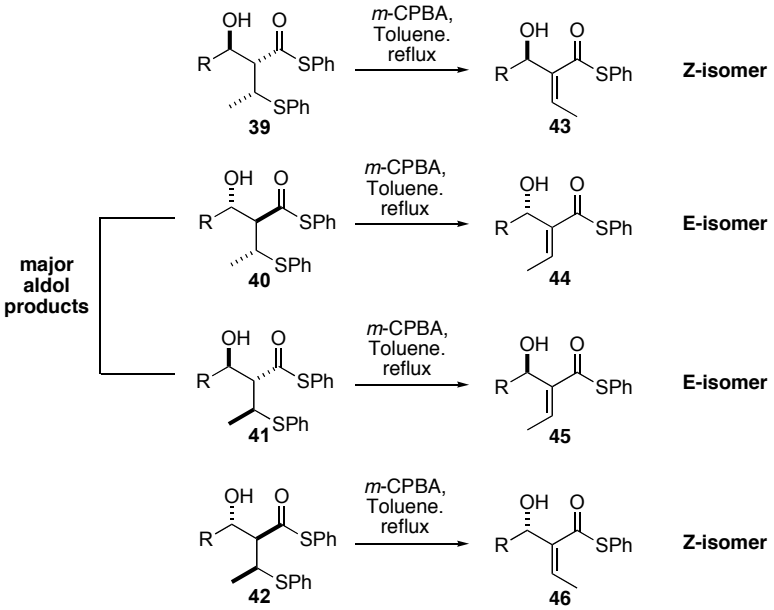


Scheme 9. Stereochemical Model of the Aldol Addition with Crotonoyl Chloride

The E-(*O*)-enolate formed from addition to the top face of crotonoyl chloride can add to the aldehyde from the front or back yielding two aldolates (**35** or **36**, respectively) as depicted in Scheme 10. In the case where the methyl group is pointing out the top face of the enolate, the more stable aldolate is that resulting from approach of the aldehyde from behind (**36**). In the case where the methyl group is pointing behind the plane, the aldehyde approaches from the front (**37**). Scheme 9 illustrates the major and minor aldolate products for both E-(*O*)-enolates. Both major products are enantiomers of each other. The same is true of the two minor products, thus accounting for the two diastereomers produced by the aldol reaction.

As indicated above, the ratio of diastereomers resulting from the aldol addition step is maintained through the oxidative elimination step. When the aldol products are

oxidized to the sulfoxides and then heated to reflux, they undergo a stereospecific concerted syn-elimination generating an olefin. This reaction destroys the two stereogenic centers at the α- and β- positions, but introduces a nonsymmetrical double-bond geometry. Sulfoxide eliminations proceed in a concerted *syn*-fashion, and thus, require a *cis*-relative orientation between the sulfoxide and relevant hydrogen. Consequently, they are stereospecific reactions. As illustrated in Scheme 10, the major diastereomer of the aldol addition each results in the *E*-configured olefin following the oxidative elimination. In contrast, the minor diastereomer gives rise to the *Z*-configured olefin.



Scheme 10. Stereochemical Outcome of the Oxidative Elimination

1.3 Conclusion

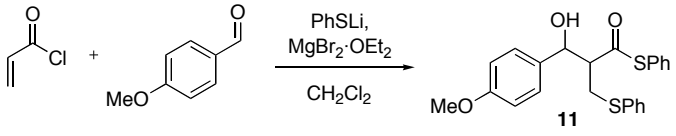
In Conclusion, we have developed a reliable, practical, and general alternative to MBH reaction that provides straightforward access to α-alkenyl-β'-hydroxy thioesters. Unlike the traditional MBH reaction, this procedure is consistently rapid and high yielding and is amenable to the use of both electron-rich and electron-poor aldehydes. Moreover, it can be applied in situations involving both sterically hindered aldehydes and β-substituted α,β-unsaturated acid chlorides, thus providing access to structures that would be difficult or impossible to generate using conventional MBH reaction conditions.

1.4 Experimental Section

General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et_2O, CH_2Cl_2, THF, MeCN, and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for

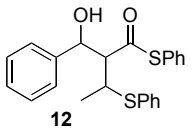
routine purposes without further purification. Et_3N, pyridine, *i*-Pr_2NEt, 2,6-lutidine, *i*-Pr_2NH, and TMEDA were distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR were recorded on a 400 MHz spectrometer at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS; ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). Compounds **3**, **7**-**10** were prepared according to our previously reported method [35].

The following reaction is representative of the aldol addition reactions depicted in Table 2:



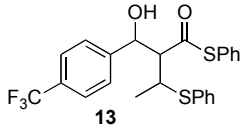
β-Hydroxy thioester (11). PhSLi (7.4 ml of a 1.0 M solution in THF, 7.4 mmol) was added slowly over 5 min to a stirred solution of acryloyl chloride (0.25 mL, 2.5 mmol), *p*-anisnaldehyde (0.20 mL, 1.6 mmol), and $MgBr_2OEt_2$ (1.73 g, 6.7 mmol) in dichloromethane (10 ml). Stirring was continued for 1 h, after which the reaction was quenched with 10% HCl (10 mL). The mixture was diluted in EtOAc, the organic layer was washed with brine (2 x 5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **11** (0.535 g, 80%) as a pure, white solid. **^1H NMR** ($CDCl_3$, 400 MHz): δ 7.40-6.89 (m, 14H), 4.92 (app. t, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.26-3.21 (m, 1H), 3.14 (dd, *J* = 8.8, 13.2 Hz, 1H), 2.97 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.78 (d, *J* = 5.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.0, 159.7, 135.4, 134.6, 133.5, 130.1, 129.8, 129.5, 129.3, 127.9, 127.7,

126.8, 114.3, 74.8, 60.1, 55.6, 33.5; **ESI/MS** m/z calcd for $C_{23}H_{22}NaO_3S_2$ (M + Na): 433.1, found 433.1.



12

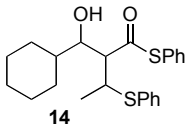
β-Hydroxy thioester (12). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **12** (0.272 g; 71%) as a colorless oil consisting of a mixture of diastereomers (2:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40-7.16 (m, 15H), 5.37-5.14 (m, containing a t at 5.35, *J* = 6.6 Hz, and a t at 3.16, *J* = 6.6 Hz, 1H), 3.50-3.43 (m, 1H), 3.35-3.19 (m, 1H, containing a d at 3.34, *J* = 8.0 Hz, and a d at 3.20, *J* = 7.6 Hz), 3.16-3.10 (m, 1H), 1.46-1.37 (m, containing a d at 1.45, *J* = 6.8 Hz, and a d at 1.38, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.3, 200.2, 141.9, 141.8, 134.8, 134.0, 133.6, 132.9, 130.1, 129.7, 129.6, 129.5, 129.0, 128.4, 128.2, 127.8, 127.7, 127.6, 126.5, 73.7, 73.6, 65.2, 64.7, 44.0, 43.2, 20.8, 19.5; **ESI/MS** m/z calcd for $C_{23}H_{22}NaO_2S_2$ (M + Na): 417.1, found: 417.1.



13

β-Hydroxy thioester (13). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **13** (0.491 g; 83%) as colorless oil consisting of a mixture of diastereomers (2:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.60-7.13 (m, 14H), 5.44-5.18 (m, containing a br. s at 5.41 and a br. s at 5.20, 1H), 3.60-3.55 (m, 1H), 3.50-3.33 (m,

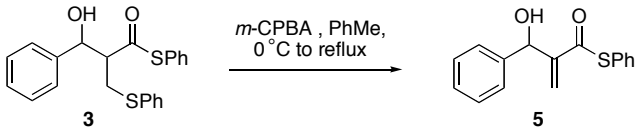
containing a br. s at 3.48, and a br. s at 3.34, 1H), 3.15-3.04 (m, containing a dd at 3.13, J = 4.4, 8.0 Hz, and a dd at 3.06, J = 4.4, 8.4 Hz, 1H), 1.52-1.42 (m, containing a d at 1.51, J = 6.8 Hz, and a d at 1.43, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.9, 146.2, 135.5, 134.7, 133.8, 133.7, 132.8, 130.6, 130.2, 129.7, 129.5, 128.4, 128.0, 127.4, 127.0, 126.9, 125.8, 123.3, 73.1, 73.0, 64.8, 64.6, 58.7, 44.0, 43.4, 20.6, 19.8, 18.7; **ESI/MS** m/z calcd for $C_{24}H_{27}F_3NaO_2S_2$ (M + Na): 485.1, found: 485.1



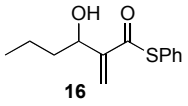
14

β-Hydroxy thioester (14). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **14** (0.399 g; 61%) as colorless oil consisting of a mixture of diastereomers (2:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50-7.26 (m, 10H), 4.00-3.49 (m, containing an apparent t at 3.97, J = 9.8 Hz, and an apparent t at 3.52, J = 10.8 Hz, 1 H), 3.81-3.72 (m, 1 H), 3.05-2.98 (m, 1H), 2.52-2.43 (m, containing a d at 2.50, J = 10.8 Hz, and a d at 2.45, J = 9.6 Hz, 1H), 2.08-0.93 (m, containing a d at 1.43, J = 7.2 Hz, and a d at 1.40, J = 6.4 Hz, 14H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.8, 135.0, 133.2, 130.4, 130.0, 129.6, 128.4, 128.0, 127.8, 76.7, 76.2, 59.8, 44.7, 43.2, 30.6, 30.1, 26.9, 26.5, 26.4, 21.1, 20.2, 14.8; **ESI/MS** m/z calcd for $C_{23}H_{28}NaO_2S_2$ (M + Na): 423.2, found: 423.1.

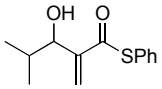
The following reaction is representative of the oxidative-elimination reactions depicted in Table 2:



α-Alkenyl β′-hydroxy thioester (5). *m*-CPBA (0.042 g, 0.181 mmol) was added to a stirred solution of α-hydroxy thioester **3** (0.06 g, 0.161 mmol) in toluene (5 ml) at 0 °C. The mixture was then heated to reflux, stirred for 30 minutes, allowed to cool to rt, and partitioned between EtOAc and 1 M Na_2SO_4. The organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **10** (0.042 g, 96%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37-7.22 (m, 10H), 6.43 (s, 1H), 5.95 (s, 1H), 5.58 (d, *J* = 5.0 Hz, 1H), 2.85 (d, *J* = 5.0 Hz, 1H) ; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.6, 150.0, 141.3, 135.6, 130.3, 129.9, 129.2, 128.7, 127.5, 127.3, 125.4, 74.0; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 293.1, found: 293.0.

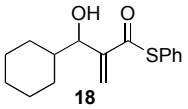


α-Alkenyl β′-hydroxy thioester (16). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **16** (0.036 g; 77%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.49-7.39 (m, 5H), 6.35 (s, 1H), 5.97 (s, 1H), 4.46 (q, *J* = 6.4 Hz, 1H), 2.31 (d, *J* = 6.4 Hz, 1H), 1.57-1.25 (m, 4H), 0.932 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 192.5, 150.4, 135.2, 129.8, 129.4, 127.2, 123.6, 72.0, 38.5, 19.1, 14.0; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 259.1, found: 259.0.



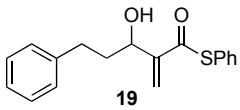
17

α-Alkenyl β′-hydroxy thioester (17). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **17** (0.046 g; 84%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.48-7.43 (m, 5H), 6.36 (s, 1H), 5.92 (s, 1H), 4.17 (apparent br. s, 1H), 2.40 (br. s, 1H), 1.95-1.88 (m, 1H), 0.93 (dd, *J* = 6.8, 10.8 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.7, 149.3, 135.1, 129.8, 129.5, 127.3, 124.6, 32.9, 19.7, 17.5; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 259.1, found: 259.0.



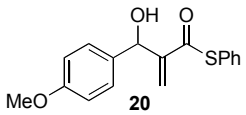
18

α-Alkenyl β′-hydroxy thioester (18). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **18** (0.030 g; 81%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.26 (m, 5H), 6.37 (s, 1H), 5.89 (s, 1H), 4.14 (apparent t, *J* = 6.8 Hz, 1H), 2.32 (d, *J* = 6.8 Hz, 1H), 1.93-1.57 (m, 6H), 1.26-0.96 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.7, 148.9, 135.1, 129.8, 129.5, 124.9, 42.5, 30.1, 28.3, 26.5, 26.3, 26.1; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 299.1, found: 299.1.



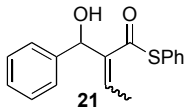
19

α-Alkenyl β′-hydroxy thioester (19). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **19** (0.070 g; 88%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.20 (m, 10H), 6.35 (s, 1H), 5.97 (s, 1H), 4.47 (dd, *J* = 4.8, 8.0 Hz, 1H), 2.84-2.64 (m, 2H), 2.03-1.89 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.0, 150.5, 142.1, 135.6, 130.3, 129.9, 129.12, 129.07, 127.6, 126.6, 124.4, 72.0, 38.3, 32.7; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 321.1, found: 321.0.



20

α-Alkenyl β′-hydroxy thioester (20). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **20** (0.028 g; 99%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.41-6.66 (m, 9H), 6.44 (s, 1H), 6.99 (s, 1H), 5.57 (d, *J* = 4.4 Hz, 1H), 3.80 (s, 3H), 2.71 (d, *J* = 4.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.0, 159.5, 149.8, 135.1, 133.0, 129.7, 129.4, 128.2, 127.1, 124.4, 114.1, 73.1, 55.5; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 323.8, found: 323.1.

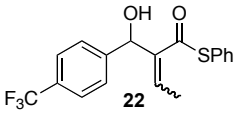


21

α-Alkenyl β′-hydroxy thioester (21, major). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave the major diastereomer of **21** (0.040 g; 70%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.38-7.20 (m, 11H), 5.73 (d, *J* = 10.8

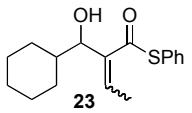
Hz, 1H), 3.82 (d, *J* = 10.8 Hz, 1H), 2.03 (d, *J* = 7.2 Hz, 3H) ; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.7, 142.2, 141.9, 140.1, 135.4, 129.8, 129.4, 128.7, 127.5, 127.3, 125.6, 70.6, 14.9; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 307.1, found: 307.1.

α-Alkenyl β′-hydroxy thioester (21, minor). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave the minor diastereomer of **21** (0.015 g; 26%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40-7.26 (m, 10H), 6.10 (q, *J* = 7.2 Hz, 1H), 5.55 (br. s, 1H) 2.66 (d, *J* = 4.8 Hz, 1H), 2.03 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.4, 142.9, 141.3, 134.9, 133.2, 129.8, 129.5, 128.7, 128.2, 127.5, 127.0, 75.7, 15.9; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 307.1, found: 307.1.



22

α-Alkenyl β′-hydroxy thioester (22). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **22** (0.050 g; 94%) as a colorless oil consisting of a mixture of diastereomers (2.3:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.59-6.11 (m, containing a q at 6.14, *J* = 7.2 Hz, 10 H), 5.78-5.55 (m, containing a d at 5.77, *J* = 10.8 Hz, and a d at 5.56, *J* = 5.2 Hz, 1H), 3.88-2.86 (m, containing a d at 3.86, *J* = 10.8 Hz, and a d at 2.88, *J* = 5.6 Hz, 1H), 2.10-2.07 (m, containing a d at 2.09, *J* = 7.2 Hz, and a d at 2.08, *J* = 7.2 Hz, 3H) ; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.2, 146.7, 141.8, 141.3, 135.8, 135.2, 134.9, 130.4, 129.9, 127.5, 127.3, 126.3, 126.0, 75.9, 70.5, 16.5, 15.4; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 375.06, found: 375.0.



23

α-Alkenyl β′-hydroxy thioester (23). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **23** (0.027 g; 88%) as a colorless oil consisting of a mixture of diastereomers (2.2:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.45-7.43 (m, 5H), 7.14-6.00 (m, containing a q at 7.11, *J* = 7.2 Hz, and a q at 6.03, *J* = 7.2 Hz, 1H), 4.21-3.96 (m, containing an apparent t at 4.19, *J* = 10.2 Hz, and an apparent t at 3.98, *J* = 6.8 Hz, 1H), 3.09-2.12 (m, containing a d at 3.08, *J* = 10.4 Hz, and a d at 2.13, *J* = 6.8 Hz, 1H), 2.03-1.94 (m, containing a d at 2.02, *J* = 7.2 Hz, and a d at 1.95, *J* = 7.2 Hz, 3H), 1.78-0.80 (m, 11H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.3, 141.6, 139.8, 136.8, 135.4, 134.8, 133.8, 131.6, 129.7, 129.6, 129.4, 129.0, 127.7, 127.6, 74.6, 43.0, 30.1, 29.7, 26.6, 26.2, 26.0, 14.9; **ESI/MS** m/z calcd for $C_{19}H_{22}NaO_2S_2$ (M + Na): 313.1, found: 313.1.

2. Studies on the Asymmetric Total Synthesis of Apratoxin D

2.1 Background and Introduction

2.1.1 Isolation and Biological Information

Apratoxins A-E (**47**-**51**, Figure 3) are a family of cyclic depsipeptides isolated from cyanobacteria of the *Lyngbya* species [43-46]. Not only are these natural products interesting from a structural point of view, but they are also compelling targets to study on the basis of their biological activity. They exhibit potent (low nanomolar) inhibition of cancer cell growth by inducing G1 phase cell cycle arrest and apoptosis [47]. The apratoxins are of mixed biogenetic origin [43-46], containing both polyketide and polypeptide fragments.

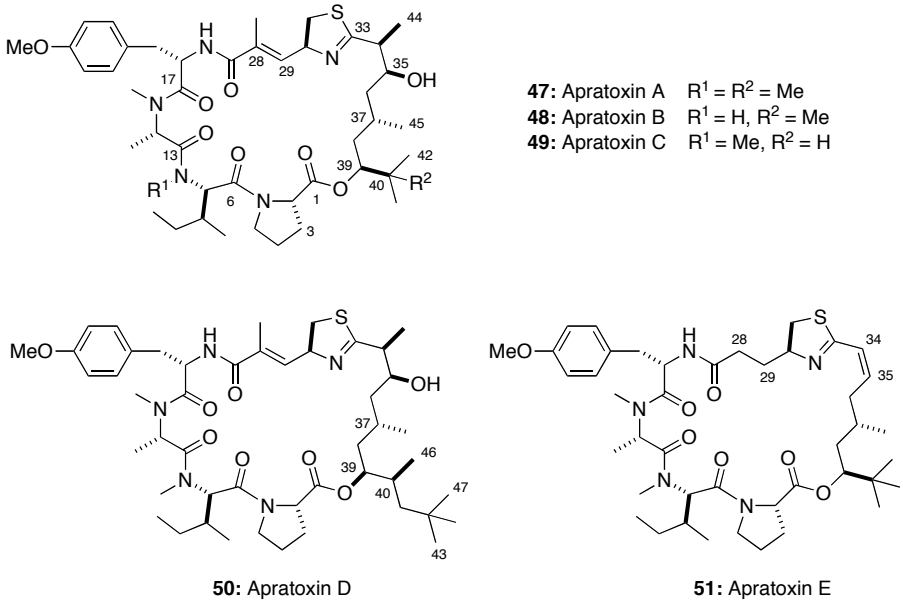


Figure 3. Structures of Apratoxins A-E

Apratoxin A (**47**) was isolated from the marine cyanobacterium *Lyngbya majuscula* in Guam by Moore, Paul, and co-workers[43], Apratoxins B and C, were isolated one year later from further collections of the cyanobacteria [44], These naturally occurring analogues differ only slightly from apratoxin A, with apratoxin B lacking a *N*-methyl group on the isoleucine residue and apratoxin C containing an isopropyl group in place of the *tert*-butyl group at C-39. Apratoxin A shows potent in vitro cytotoxicity against both KB (0.52 nM) and LoVo (0.36 nM) cell lines, but was poorly tolerated in mice, mainly due to lack of selectivity [43, 44], Apratoxins B (**48**) and C (**49**) both displayed weaker cytotoxicity than A; however, while C closely approached the IC_{50} value of apratoxin A, apratoxin B showed significantly less activity. These differences in activity indicate that the *tert*-butyl group is not essential for cytotoxicity, as replacing it with the somewhat less sterically demanding isopropyl group has a minimal effect on activity [44]. In addition, the substantial difference in activity exhibited by apratoxin B indicates that the *N*-methyl group at the isoleucine residue might be necessary for cytotoxic activity.

Apratoxin E (**51**) was isolated from the marine cyanobacterium *Lyngbya bouillonii* in 2008 [46]. Like apratoxin A, this compound contains the *N*-methylated isoleucine as well as the *tert*-butyl group at C39. However, compared to A, apratoxin E is unsaturated at the C34–C35 bond alpha to the thiazoline moiety and lacking a methyl group at C34. In addition, the modified cysteine residue is fully saturated at C28–C29 and lacks a C28 methyl group. When tested for activity against several human cancer cell lines including HT29 colon adenocarcinoma, HeLa cervical carcinoma, and U2OS osteosarcoma cells, apratoxin E exhibited strong cytotoxicity (21-72 nM); however, this was 5- to 15-fold less active than apratoxin A (1.4-10 nM) [46].

Apratoxin D (**50**) was isolated from two species of cyanobacteria, *L. majuscula* and *L. sordida* in 2008 [45]. Structural analysis revealed that apratoxin D has the same

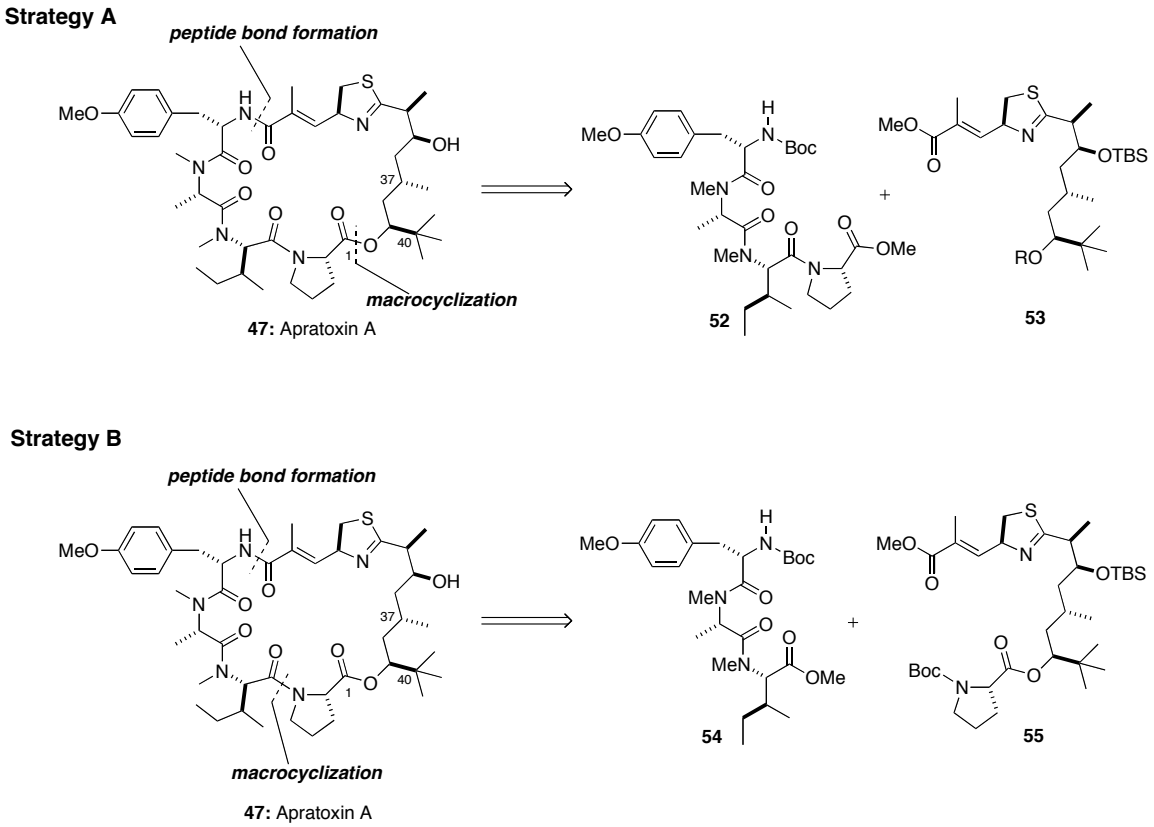
sequence of amino acid residues as A and C, but its polyketide moiety is longer than that of the other apratoxins. Apratoxin D showed potent in vitro cytoxicity against H-460 human lung cancer cells with an IC_{50} value of 2.6 nM. This activity is nearly the same as apratoxin A, indicating that the activity of the compound is not negatively impacted by the longer alkyl group at C39. This suggests that the C39 alkyl chain can potentially be varied in the design of structural analogues to improve activity or provide insight into the mechanism of action of this family of compounds.

The extremely promising biological activity of the apratoxins, as well as the small amounts available via isolation from natural sources, make them very compelling lead compounds for the development of anti-tumor drugs via asymmetric total synthesis. By developing synthetic routes to these newly isolated compounds (apratoxins D and E), as well as structurally modified versions, we can probe the mechanism of action to fully develop their biomedical potential. The following project focuses only on the total synthesis of apratoxin D, but is based on a method that can potentially also be used to synthesize apratoxin E as well as other structural variants.

2.1.2 Prior Synthetic Work

Three total syntheses of apratoxin A have been reported, one by Forsyth,[48, 49] Takahashi [50], and Ma [51]. As outlined in Scheme 11, apratoxin A could logically be disconnected to yield tetrapeptide **52** and the thiazoline containing polyketide (**53**). However, one strategy common to all three syntheses for merging the peptide and polyketide domains is the early incorporation of the proline residue as the C39 ester (**55**). This strategy was utilized in anticipation of a higher yielding amide formation between the isoleucine carboxylate of tripeptide **54** and proline amine moieties in comparison to the condensation between the proline carboxylate of **52** and the hindered

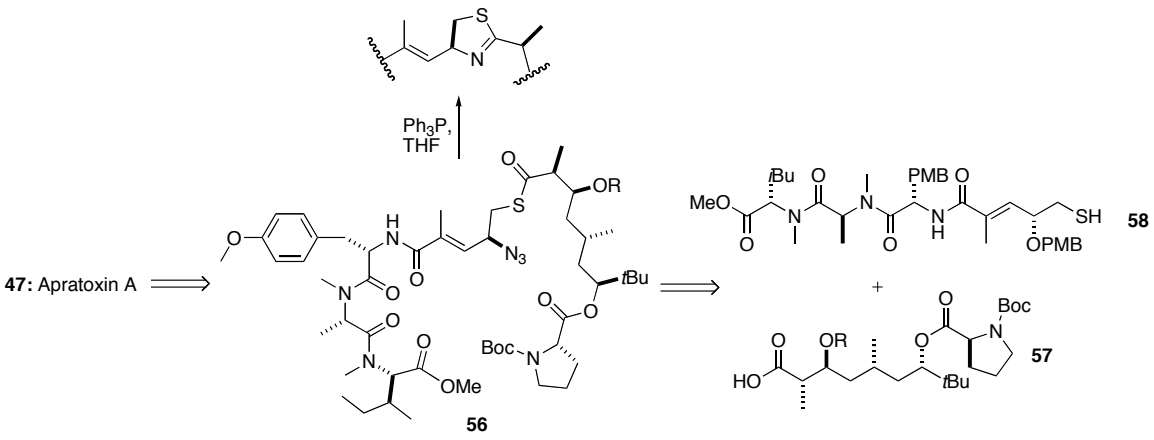
C39 hydroxyl of **53** [48-51]. Also common to the three prior syntheses is the late stage assembly of the thiazoline moiety, which is oxidatively sensitive and potentially prone to unwanted side reactions. While the tripeptide (**54**) can theoretically be accessed in a relatively straightforward way using standard peptide synthesis procedures, the polyketide and thiazoline portions of the molecule present a significant synthetic challenge, necessitating the development of new strategies for their synthesis.



Scheme 11. Retrosynthetic Analysis of Apratoxin A

Forsyth's strategy for constructing the sensitve thiazoline moiety was a one-pot Staudinger reduction/intramolecular aza-Wittig of an α-azido thioester (Scheme 12).

Exposure to Ph_3P generated the phosphinimine from the azide in situ, which could then undergo the aza-Wittig with the adjacent carbonyl of the thioester to generate the thiazoline [49, 52, 53].

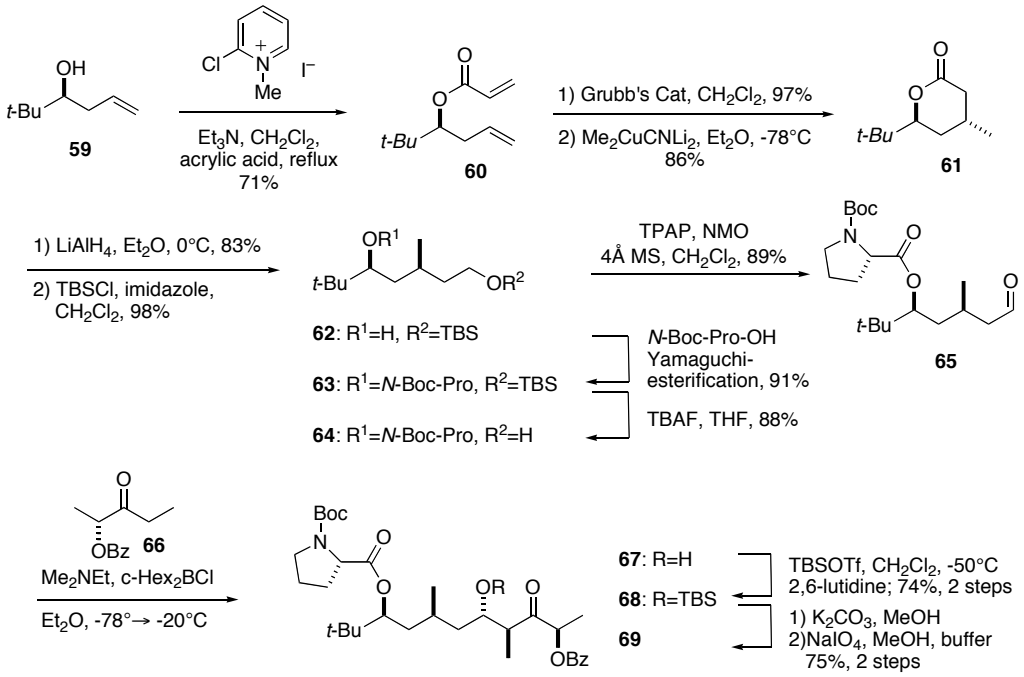


Scheme 12. Thiazoline Formation via Staudinger Reduction/Intramolecular Aza-Wittig

This strategy for thiazoline formation required an advanced intermediate containing the essential α-azido thioester (Scheme 12, compound **56**). Advanced intermediate **56** was constructed from triamide **58** and polyketide **57** (see below).

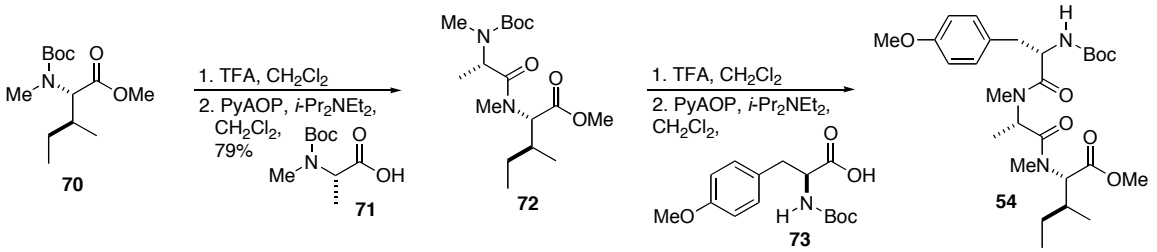
As outlined in Scheme 13, the synthesis of **57** began with acylation [54] of compound **59 [55]** with acrylic acid yielding diene **60.** Ring closing metathesis [56] of **60** gave an α,β-unsaturated δ-valeryl lactone, which upon methyl cuprate addition provided the C37 methyl group in **61**. The lactone was then reductively opened and the primary alcohol was TBS-protected to give secondary alcohol **62**. The hydroxyl group was then esterified with *N*-Boc-L-proline under Yamaguchi conditions [57] followed by TBS group removal and oxidation of the resulting primary alcohol (**64**) to the aldehyde (**65**). An *anti*-selective aldol reaction of aldehyde **65** with (*R*)-2-benzoyloxy-3-pentanone (**66**) provided β-hydroxy ketone **67**. Compound **67** was TBS protected and the

benzoyloxy-containing functionality was removed to give the target compound (**69**), the TBS protected version of fragment **57**.



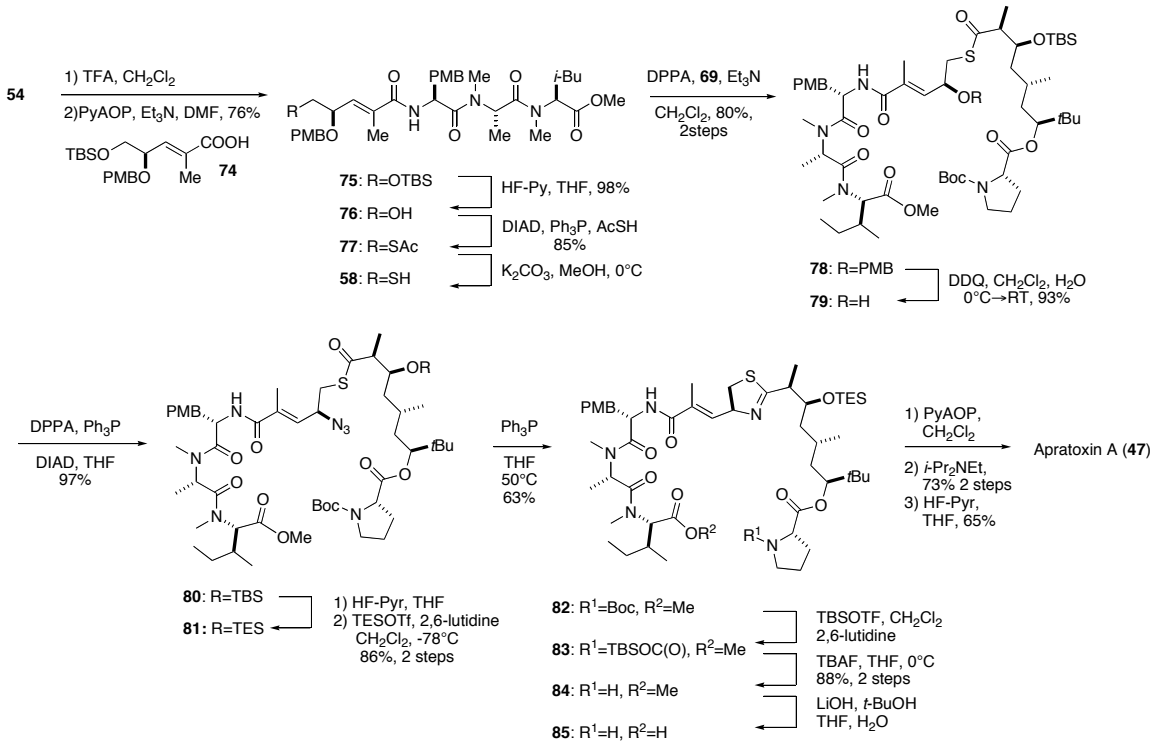
Scheme 13. Synthesis of Compound 69

The triamide (**54**) was assembled in a C→N fashion beginning with isoleucine derivative **70** (Scheme 14). Compound **70** was deprotected and coupled with Boc-protected *N*-methyl-L-alanine to yield compound **72**. Boc removal followed by a second PyAOP-mediated condensation with tyrosine derivative **73** gave triamide **54**.



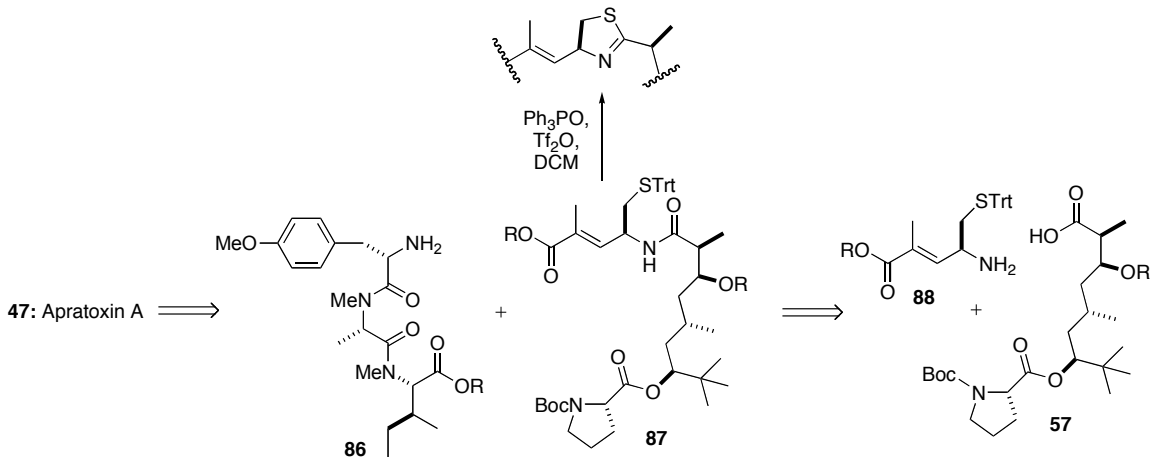
Scheme 14. Synthesis of Tripeptide 54

To carry out the intended Staudinger reduction/aza-Wittig strategy for thiazoline formation, triamide **54** had to be joined with modified cysteine surrogate **74** to form **75**, which was converted to thiol **58** in a stepwise fashion. Thioester formation between **58** and **69** followed by deprotection of the C30 hydroxyl and treatment with diphenyl phosphoryl azide under Mitsunobu conditions yielded azido thioester **79**. Because their attempts to remove the C35 TBS group at the ultimate stage of the total synthesis were unsuccessful, this protecting group was switched to a TES group at the stage of compound **79** to give **80**. Thiazoline formation was then carried out using Ph_3P giving compound **81**. Conversion of *N*-Boc protected compound **81** to the silyl carbamate followed by selective desilylation gave compound **83**. Saponification of the isoleucine methyl ester and macrolactam formation afforded cyclic depsipeptide **83**. TES group removal yielded apratoxin A (**47**).



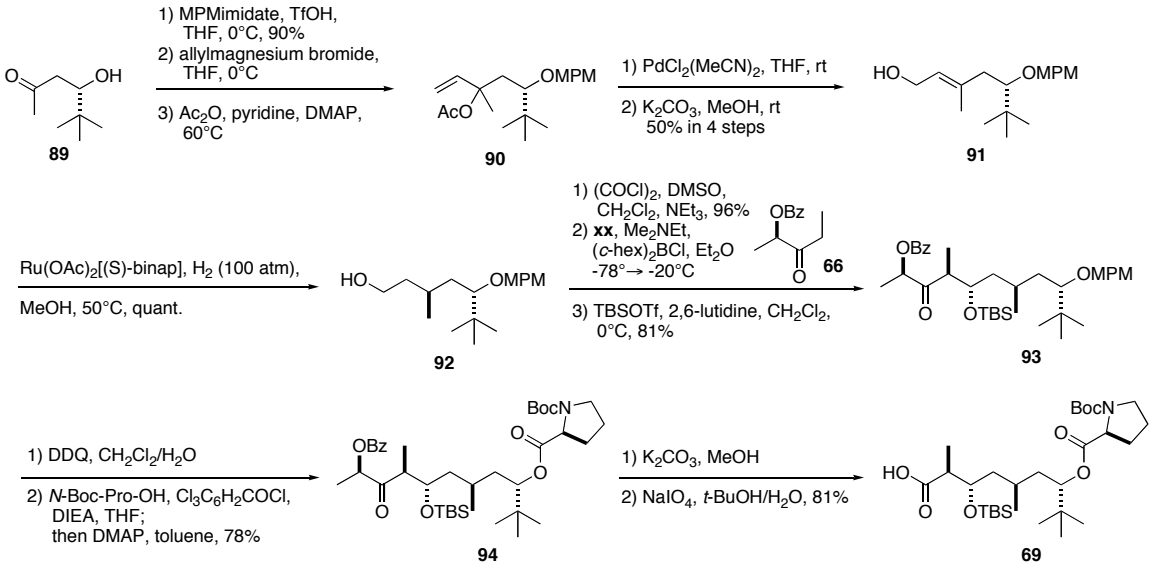
Scheme 15. Convergent Synthesis of Apratoxin A

Both Takahashi and Ma assembled the thiazoline unit using a tandem deprotection/cyclodehydration strategy [50, 51]. This strategy required the coupling of carboxylic acid **57** with modified cysteine **88** to form the trityl protected thiol amide **87**.



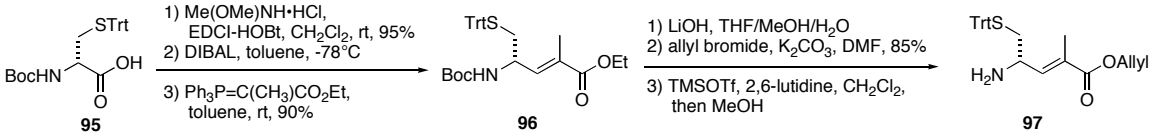
Scheme 16. Thiazoline Formation via Tandem Deprotection/Cyclodehydration

Takahashi approached the synthesis of fragment **57** starting with compound **89**, the product of a proline-catalyzed aldol reaction between acetone and pivaldehyde [58]. MPM protection followed by subsequent allylation and acetylation provided **90**. Palladium(II)-catalyzed isomerization of allylic acetate **90** and removal of the acetyl group gave alcohol **91**, which was asymmetrically hydrogenated to set the C37 stereocenter (compound **92**). Alcohol **92** was then oxidized to the aldehyde and subjected to a Paterson [59] *anti*-aldol reaction to set stereocenters C34 and C35, as Forsyth did. The resulting aldol product was TBS protected to give **94**. Removal of the MPM group followed by Yamaguchi coupling [57] with *N*-Boc-Pro-OH provided compound **94**. As with Forsyth's method, removal of the benzoate and oxidative cleavage of the resulting α-hydroxy ketone provided acid **68**, as previously reported [48].



Scheme 17. Takahashi Synthesis of Comound 69

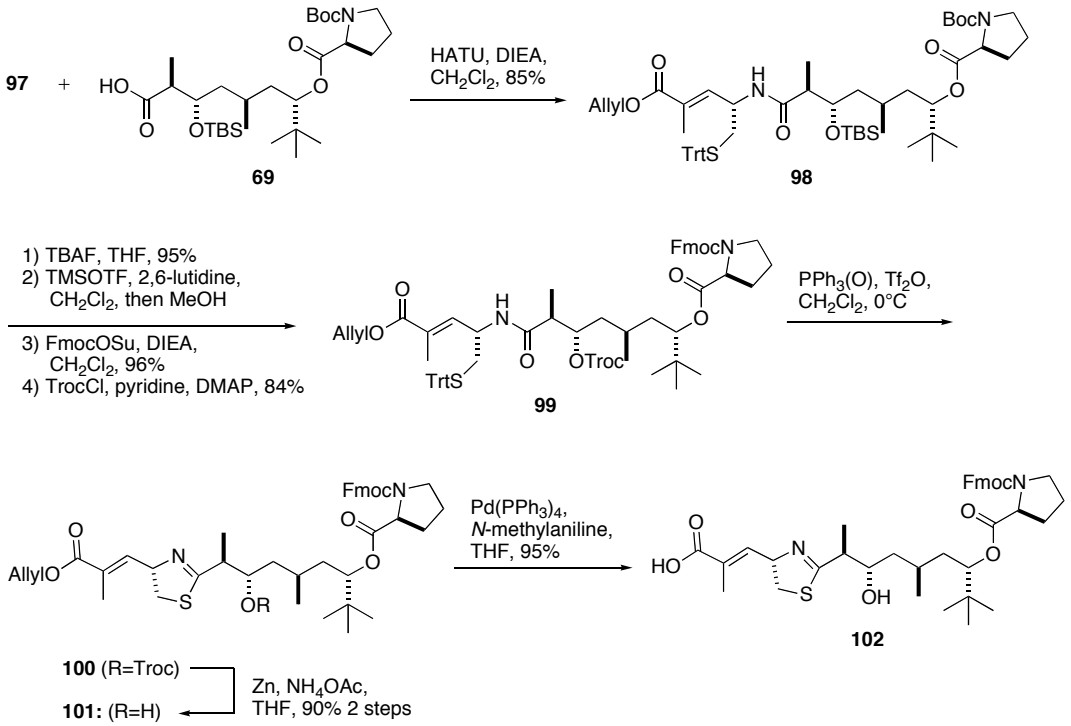
To prepare the modified cysteine residue (**97**), Takahashi converted the corresponding *S*-Trt-*N*-Boc-D-Cysteine to its aldehyde via the Weinreb amide and then Wittig olefination was carried out on the aldehyde. Hydrolysis of the ethyl ester, allyl ester formation, and selective deprotection of the *N*-Boc group provided modified cysteine residue (**97**).



Scheme 18. Synthesis of Modified Cysteine 97

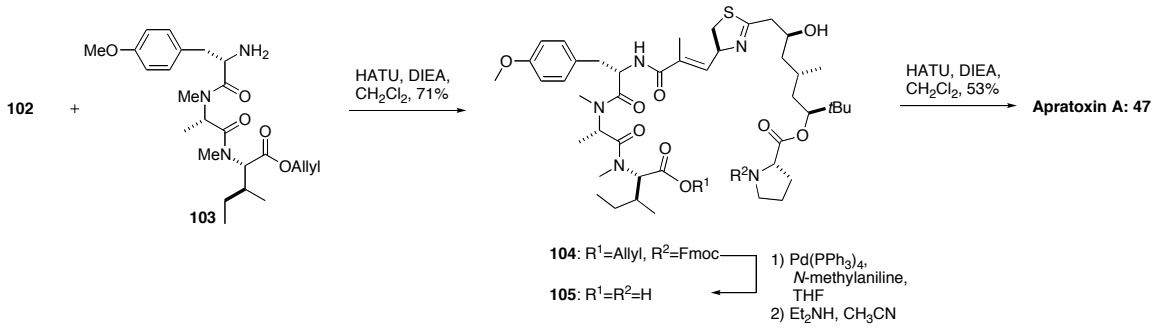
Condensation of modified cysteine residue **97** and acid **69** was followed by stepwise conversion of **98** into the corresponding 2,2,2-trichloroethoxycarbonyl(Troc) ester **99**. Thiazoline formation was then carried out via treatment of **99** with

$Ph_3P(O)/Tf_2O$. The Troc group was then removed followed by conversion of the allyl ester to the acid to afford compound **102**.



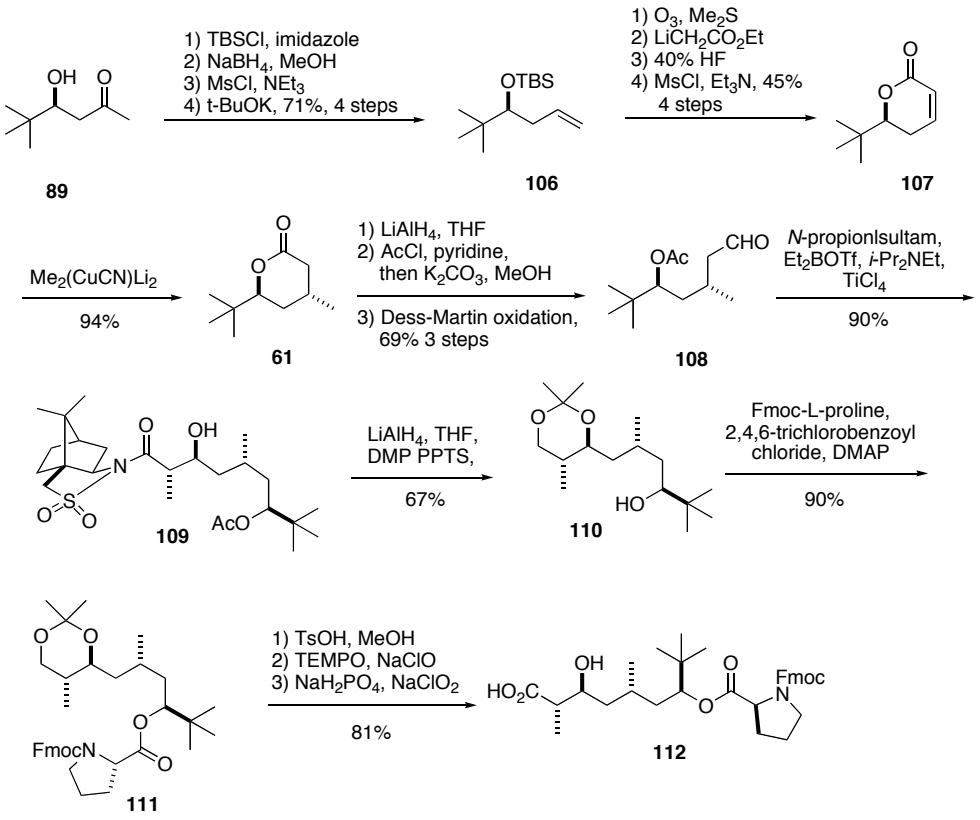
Scheme 19. Takahashi Sythesis of 102

Tripeptide **103**, prepared by sequential coupling of *N*-methylisoleucine allyl ester with *N*-Boc-*N*-methylalanine and *N*-Fmoc-*O*-methyltyrosine by repeated treatment with HATU-DIEA and ultimately Et_2NH in acetonitrile, was coupled to fragment **102** providing compound **104**. Cleavage of the allyl ester and removal of the Fmoc group afforded compound **105**, which was treated with HATU/DIEA to promote macrolactamization yielding apratoxin A (**47**).



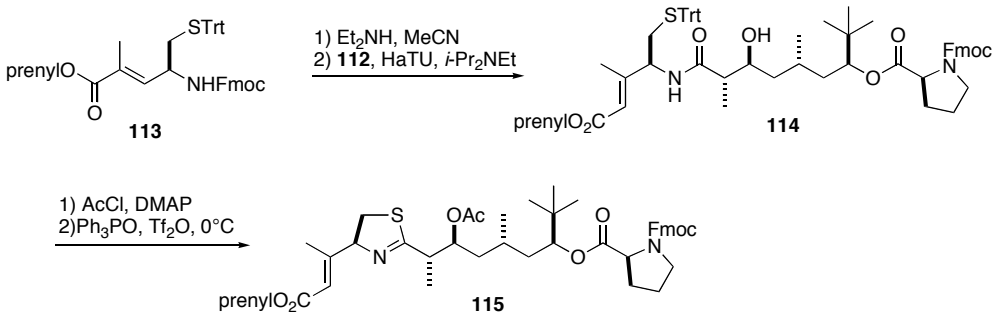
Scheme 20. Takahashi Synthesis of Apratoxin A

Because Ma's synthesis of apratoxin A employed the same strategy for thiazoline formation as Takahashi's synthesis, the initial target was fragment **112**. Their synthesis of fragment **112** began with the same proline-catalyzed aldol product (**88**) as used by Takahashi. This compound was TBS protected, reduced, and eliminated via its mesylate to give allyl ether **106**. This compound was converted to α,β-unsaturated lactone **107**, which was treated with a methyl cuprate to form **61**, setting the C37 stereocenter as Foryth [48] did. The lactone was reduced and protected as the diester with acetyl chloride, which was selectively deprotected to form the primary alcohol. The alcohol was oxidized to aldehyde **108**, which was subjected to an *anti*-aldol using Oppolzer's sultam methodology to give **109** [60]. Treatment with LAH removed both the auxiliary and the acyl group yielding a triol, which was protected with DMP to provide alcohol **110**. The Boc-protected proline was installed via Yamaguchi esterification [57], as with the other two syntheses, giving **111**. The diol was liberated, and the primary alcohol was selectively oxidized using the bulky chloro oxammonium salt generated from TEMPO/NaClO to give an aldehyde, which was subsequently oxidized to acid **112**.



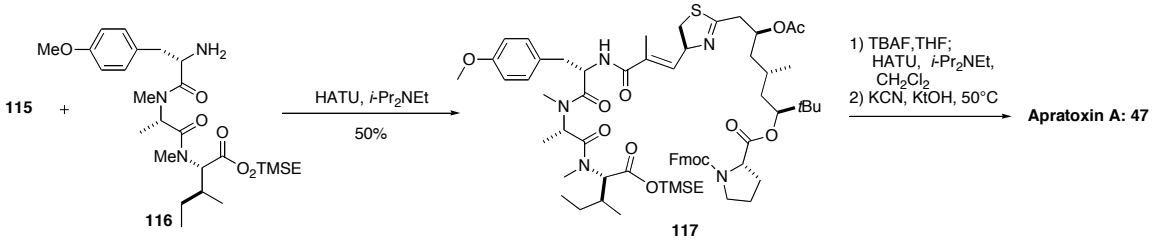
Scheme 21. Ma Synthesis of Fragment 112

The modified cysteine unit (**113**) was prepared using the same conditions as outlined in Takahashi's synthesis, but starting with Fmoc protected cysteine as apposed to the Boc-protected cysteine and generating the prenyl ester rather than the allyl. This modified cysteine (**113**) was coupled to the carboxylic acid (**112**), and the thiazoline was formed under the same conditions employed by Takahashi.



Scheme 22. Ma Synthesis of Thiazoline 115

Fragment **115** was then coupled with tripeptide **116**. Subsequent cleavage of the Fmoc and TMSE protecting groups yielded the cyclization precursor **117**. Macrolactamization followed by acyl group removal resulted in Apratoxin A (**47**).

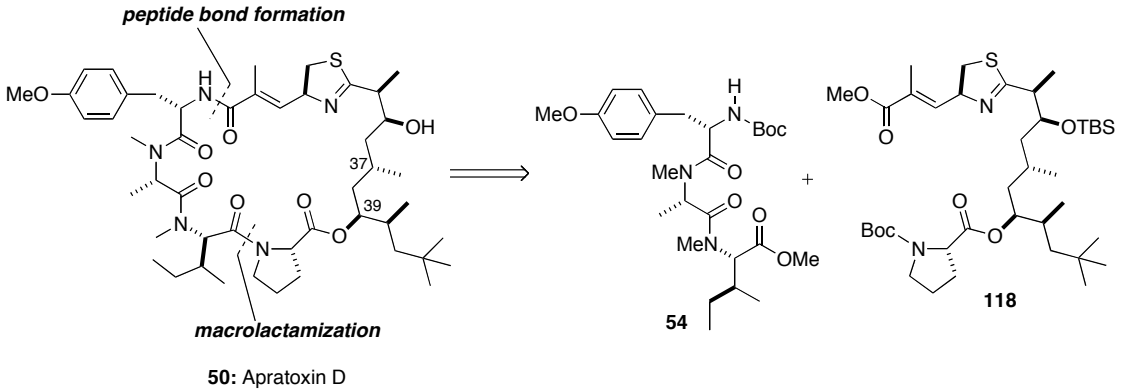


Scheme 23. Ma Synthesis of Apratoxin A

2.1.3 Retrosynthetic Analysis of Apratoxin D

We planned to synthesize apratoxin D (**50**) in a convergent manner as outlined in Scheme 24. Based on the prior synthetic work on apratoxin A, we intended to incorporate the proline residue in the polyketide fragment (**118**) and carry out the macrolactamization between the proline amine and the isoleucine carboxylate. By analogy to earlier work, this strategy would presumably be advantageous over macrolactone formation involving the proline carboxylate and sterically hindered C39 hydroxyl. Since tripeptide **54** is known, our target becomes fragment **118**.

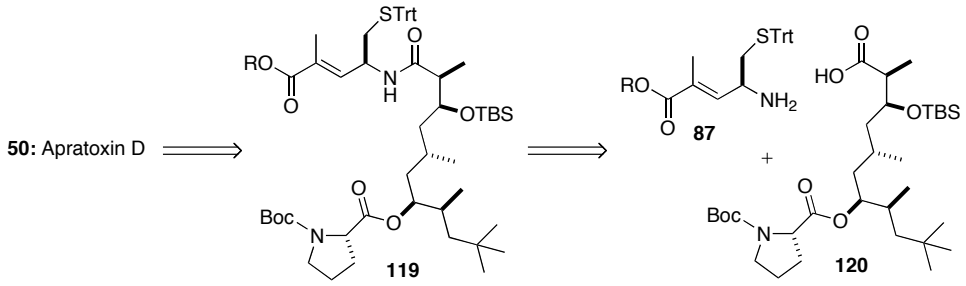
Our choice of protecting groups at this stage is very important because, ultimately, we need to be able to remove them orthogonally, meaning we can manipulate each group independently of the other. For example, by using the protecting groups outlined in Scheme 24, we can hydolyze methyl ester **118** to the acid without affecting the *N*-Boc group or the TBS protected hydroxyl. Likewise, we can deprotect Boc-protected amine **54** without affecting the isoleucine methyl ester. In this way, we can couple **54** with **118** via peptide bond formation between the free amine of **54** and carboxylic acid **118**. Subsequent deprotection of the isoleucine methyl ester and *N*-Boc proline group allows for macrolactam formation. Finally, in the last step, we can remove the silyl group.



Scheme 24. Retrosynthetic Analysis of Apratoxin D

The next synthetic challenge that would have to be addressed is formation of the oxidatively-sensitive thiazoline moiety. As described above, two different methods have been employed for thiazoline construction in earlier syntheses of apratoxins A-C. We intended to utilize the tandem deprotection/cyclodehydration strategy that both Takahashi and Ma employed [50, 51]. This strategy requires the coupling of carboxylic

acid **120** with modified cysteine **87** to form the trityl protected thiol amide **119**, which could then be converted to **50** via coupling to the tripeptide and macrolactam formation.

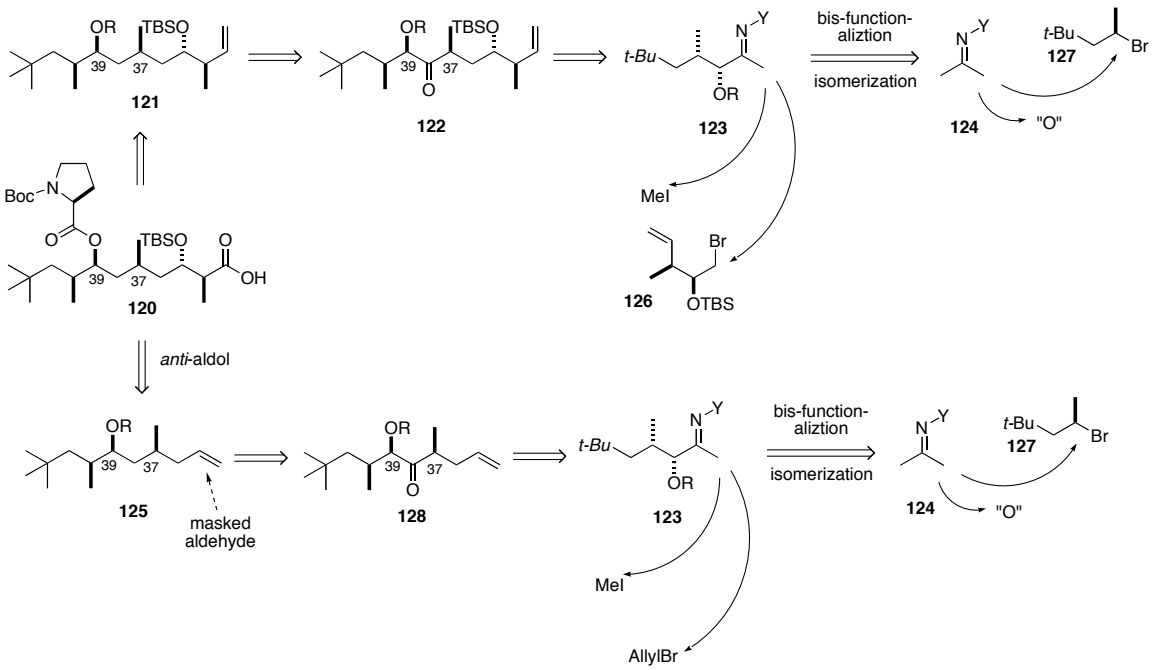


Scheme 25. Strategy for Thiazoline Formation in Apratoxin D

Compound **120** represents the key synthetic challenge associated with the synthesis of apratoxin D. To prepare this fragment, we planned to use a new method recently reported by our group for the asymmetric α,α-bisalkylation of acyclic ketones using chiral *N*-amino cyclic carbamate (ACC) hydrazones [61]. By connecting this alkylation method with known methods for the conversion of ketones to the corresponding methylene group, we can consider the C38 carbon to be a ketone. This then allows us to utilize the above mentioned asymmetric alkylation method to set the stereochemistry at C37.

Construction of fragment **120** can be achieved as outlined in scheme 26. Starting with the acetone-derived hydrazone (**124**), we can build complexity via a tetra-functionalizaton. Sequential α-alkylation and α-oxidation followed by isomerization would give compound **123**, which could then be further elaborated by an α′,α′-bisalkylation. In the second set of alkylations, hydrazone **123** would be sequentially methylated and either allylated or treated with an advanced alklylating agent (**126**) containing the stereocenters at C34 and C35. The ability to construct molecules in this way would be extremely useful, not just for this synthesis, but potentially as a general

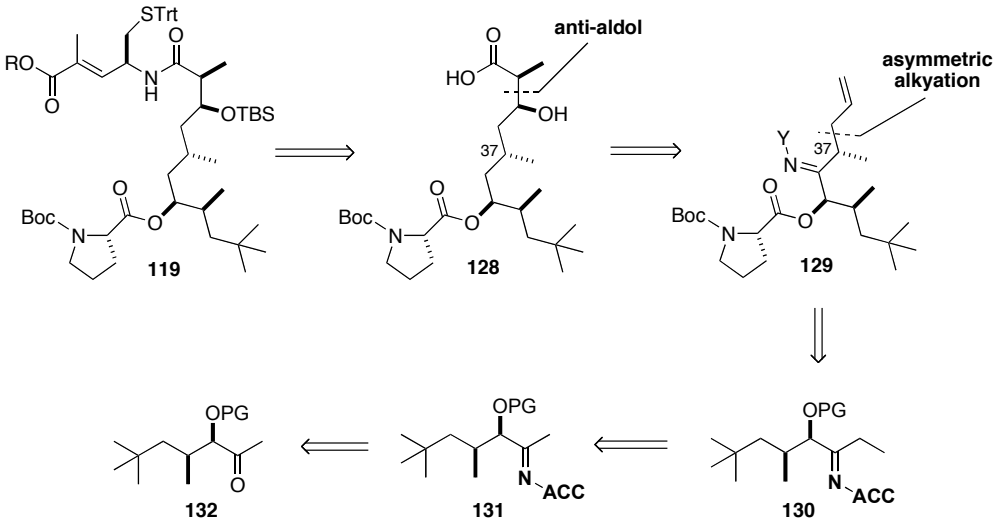
strategy for highly convergent syntheses of many types of natural products. With this in mind, we wanted to synthesize apratoxin D in this way to demonstrate whether this strategy could be applied to the synthesis of a complex molecule.



Scheme 26. Proposed Synthetic Approach of Fragment 41 Starting from Acetone Hydrazone 49

A possible limitation of the tetra-functionalization proposed above regards the second bisfunctionalization. The substrate of this transformation (**128**) possesses two stereogenic centers at C39 and C40 not associated with the ACC auxiliary. Ideally, the ACC auxiliary would be able to override any influence on the sterochemical course of the bisfunctionalization imposed by these additional stereogenic centers. However, at the outset we did not know if this would indeed be the case, as we had yet to examine our auxiliaries under such circumstances. As such, prior to embarking on the tetrafunctionalization strategy, we felt it prudent to test this. To do so, we would carry

out the α,α-bisalkylation to set the stereochemistry at C37 in a hydrazone that already contained the C39 and C40 stereogenic centers. Therefore, we set ketone **132** as our initial target. With this compound in hand, we could effect diastereoselective hydrazone formation to product compound **131**, which would then serve as our model substrate to test the bisalkylation sequence in question.



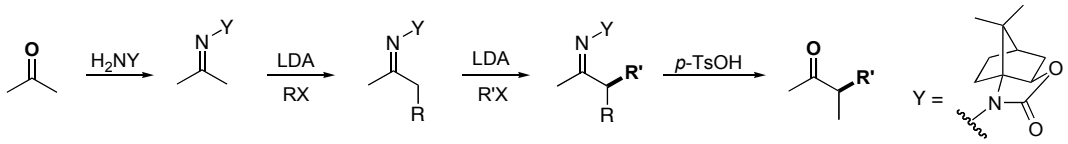
Scheme 27. Strategy for the Synthesis of Fragment 40

2.1.4 α-Alkylation of Ketones

The alkylation of ketones via electrophilic addition to derived enolates is a fundamental synthetic transformation. Azaenolates have been employed in place of enolates with several significant advantages including enhanced nucleophilic character of the anionic intermediate, greater regioselectivity for *C*-alkylation, and the potential for asymmetric induction through the use of chiral amines and their derivatives [62]. The standard method for asymmetric α-functionalization of aldehydes and ketones has been alkylation via SAMP/RAMP-derived hydrazones. These well-known dialkyl hydrazine auxiliaries are stable and give good to excellent stereoselectivity and yield [63, 64].

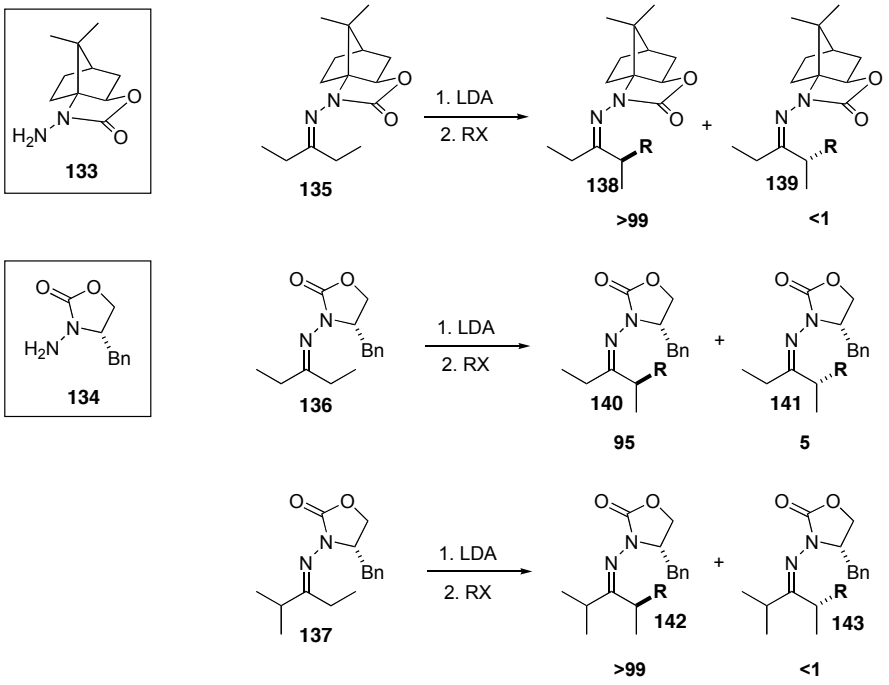
Despite the wide use of these auxiliaries, they suffer several practical limitations. For instance, the SAMP/RAMP auxiliaries are based on a proline core, which limits structural variation for improvement of selectivity, reactivity, etc., and, since their synthesis is non-trivial, they are expensive (SAMP = $120.50/g; RAMP = $116.50/g) [65]. Because the auxiliaries are liquids and the derived hydrazones generally are as well, they are somewhat difficult to work with. Moreover, formation of the corresponding hydrazones requires long periods of reflux under dehydrating conditions. Due to the weakly acidic nature of dialkyl hydrazones, azaenolate formation requires lengthy (2-10 h) exposure to LDA and, once formed, the metallated species must be cooled to an extremely low temperature (–110 °C) prior to alkylation, making large-scale applications impractical. Another limitation is that the conditions for auxiliary removal are problematic. Removal of the costly auxiliary under recommended [64] conditions (ozonolysis or quaternization/hydrolysis) limits functional group compatibility, and liberates it in an altered form that hinders recycling or makes it impossible. Moreover, under oxidative cleavage conditions aldehyde–derived hydrazones produce nitriles, not aldehydes [64].

In an effort to address some of the above-mentioned limitations, our group recently reported a method employing *N*-amino cyclic carbamates (ACCs) (Scheme 20) [61]. These activated hydrazones possess an electron withdrawing group, enhancing the acidity of the α-proton which enables rapid deprotonation (less than 1 hour at -78 °C). These auxiliaries are easily introduced into and removed from ketones, and alkylation does not require extremely low temperatures, yet proceeds with excellent stereoselectivity and yields. Furthermore, the ACC auxiliaries exhibit a unique directing effect that overrides the inherent selectivity of LDA, enabling the asymmetric α,α-bisalkylation of ketones as opposed to α,α′-bisalkylation, which would result from SAMP/RAMP hydrazones.



Scheme 28. Bisalkylation via ACC Hydrazones

Of the auxiliaries originally screened, camphorsulfonic acid derived auxiliary **61** gave the best stereoselectivity (>99:1). This compound is synthesized in 6 steps from camphorsulfonic acid. One of the other auxiliaries (**62)** examined is easily accessible in one step from the phenylalanine derived oxazolidinone, but the selectivity of this auxiliary in the context of the 3-pentanone-derived hydrazone was not quite as good as **61**, giving a dr of 95:5 (Scheme 21). However, after further mechanistic studies, it was determined that the simpler phenylalanine-derived auxiliary gave equally high selectivity in cases where there was extra steric bulk on the α' side of the hydrazone. As this is the case for the ketone (**60**) to be alkylated in the synthesis of apratoxin D, we can use the simpler, more easily accessible auxiliary.



Scheme 29. Comparison of ACC Auxiliaries

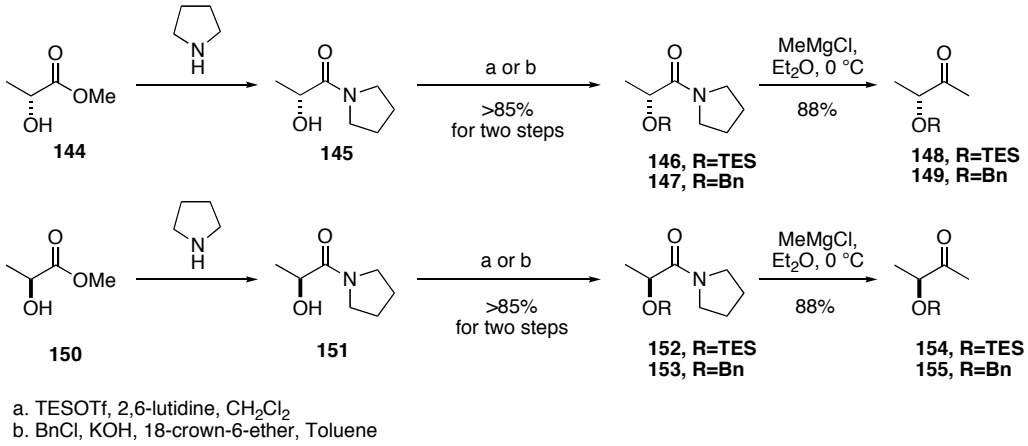
2.2 Results and Discussion

2.2.1 Model Hydrazone

As mentioned above, prior to embarking on a synthesis of apratoxin D using asymmetric tetrafunctionaliztion as the key step, we needed to test the effectiveness of our new ACC alkylation method in the context of a hydrazone substrate (**131**) having additional stereogenic centers. The chiral nonracemic ketone (**132**) needed to prepare this hydrazone possesses a stereogenic center at the α'-position. Consequently, an added challenge here is that the ACC auxiliary would have to be able to be introduced without causing epimerization at that center.

To address the latter issue, we opted for an even simpler model system based on optically pure 3-hydroxy-2-butanone (cf. **148**, **149**, **154**, **155**), which should be

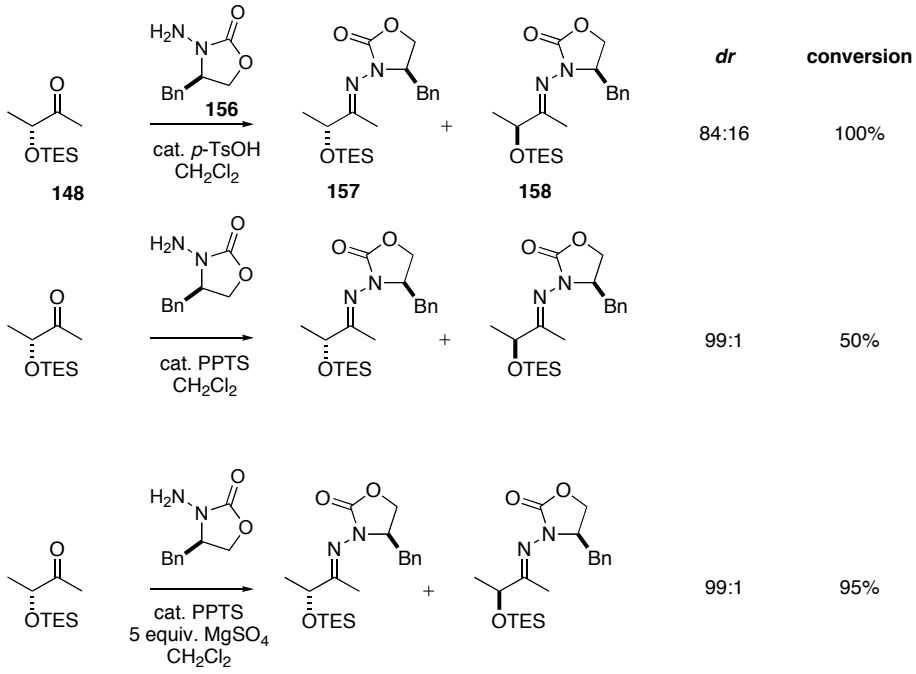
reasonably easily accessible from commercially available methyl lactate. Thus, we synthesized both the TES protected (*R*)- and (*S*)-3-hydroxy-2-butanone (**148** and **154**, respectively) starting with D- and L-methyl lactate, respectively, accorsing to a literature procedure (Scheme 30).[66, 67] Addition of MeMgCl to the corresponding pyrrolidine amides provided the ketones in high yield within 2 hours. In addition to the TES protected ketones, we also synthesized the corresponding benzyl protected systems (**149** and **155**).



Scheme 30. Synthesis of Model Ketones

Using the TES-protected α-hydroxy ketone (**76**), we attempted to form the hydrazone using *p*-TsOH in dichloromethane, conditions that we had previously used for achiral ketones (Scheme 31) [61]. Unfortunately these conditions resulted in significant epimerization of the α-position. The extent or epimerization was determined by HPLC analysis. We then switched to the weaker acid PPTS and, while the extent of empimeriztion was minimal (>99:1), we only observed 50% conversion to the product. We then attempted to promote the reaction using 5 equivalents of $MgSO_4$ as a dehydrating agent. Gratifyingly, the conversion improved to 100%. We also carried out

the hydrazone formation with the benzyl protected α-hydroxy ketones (**149** and **155**) using these conditions, however in this case some epimerization occurred and product was obtained as a 95:5 mixture of stereoisomers.



Scheme 31. Condition Screen for Hydrazone Formation in Model Ketone

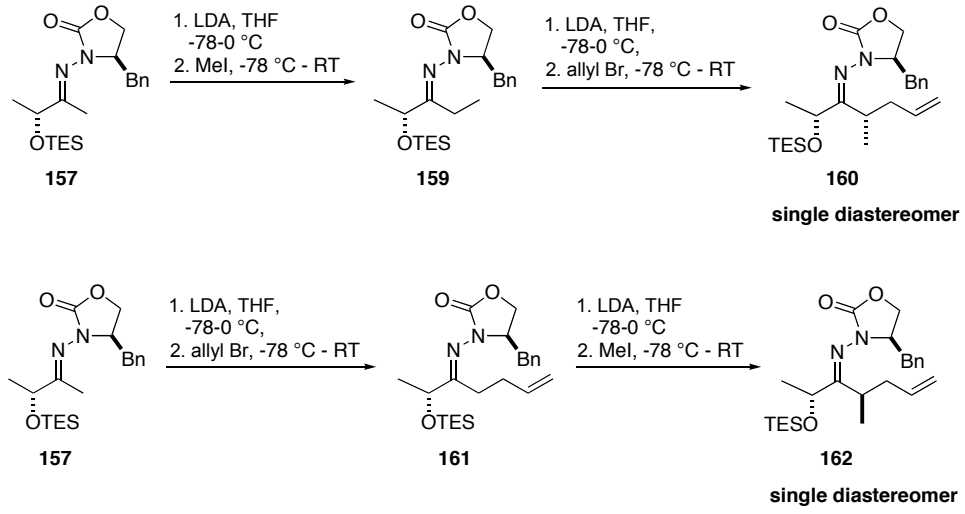
We next attempted the bis-alkylation on the model hydrazone to determine what effect the α' stereocenter would have. Using the previously established conditions for alklylating an ACC hydrazone (entry 1, Table 4) [61], methylation of hydrazone **157** was attempted; however, the reaction only proceeded with 50% conversion to the methylated product **159**. We increased the equivalents of LDA from 1.1 to 3 and the conversion increased to 75%. We then allowed the deprotonation to warm to 0°C and saw complete conversion to methylated product **159** (entry 3, Table 4). These conditions were also successful for methylating hydrazone **158**.

Table 4. Condition Screen for Methylation of ACC Hydrazone 157

157 **159**

Entry	Condtions	Conversion
1	**Deprotonation**: 1.1 equiv. LDA, -78 °C, 1 h **Alkylation**: 10 equiv. MeI, RT, 1h	50%
2	**Deprotonation**: 3 equiv. LDA, -78 °C, 1 h **Alkylation**: 10 equiv. MeI, RT, 1	75%
3	**Deprotonation**: 3 equiv. LDA, 0 °C, 1 h **Alkylation**: 10 equiv. MeI, RT, 1 h	100%

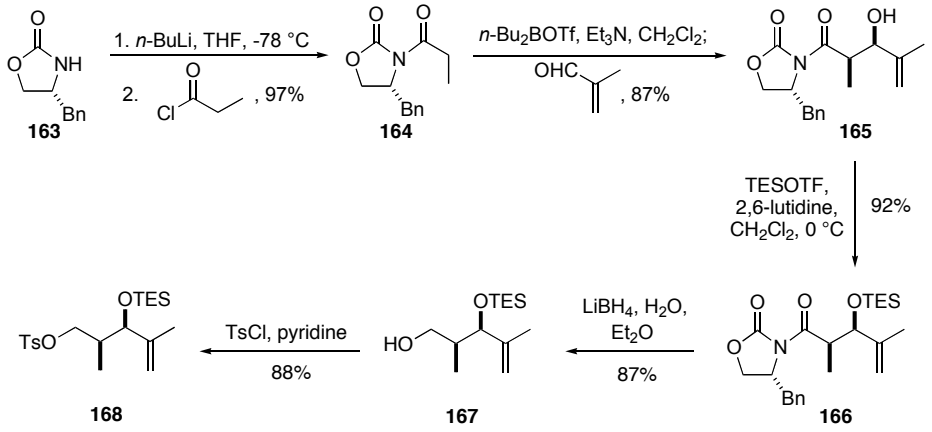
We next attempted to perform the second α-alkylation. Methylated hydrazone **157** was subjected to our optimized conditions giving the α,α-bisalkylated product in 96% yield as a single diastereomer by NMR, suggesting that the dr is at least 95:5. When the alkylations were carried out in the reverse order, the same result was observed.



Scheme 32. Bisalkylation of Model Hydrazone 157

2.2.2 Synthesis of Apratoxin D Hydrazone

With conditions for installing the auxiliary and carrying out the bis-alkylation we were ready to test the ACC method on the more complicated ketone **132**. For the synthesis of **132**, primary alcohol **167** was prepared using Evan's oxazolidinone aldol chemistry according to a four-step literature procedure (Scheme 33) [68]. The acyl oxazolidinone (**164**) was subjected to an enantioselective *syn*-aldol with methacrolein in high yield, and the resulting product was TES-protected. Hydrolysis of the TES-protected compound yielded primary alcohol **167**, which was then tosylated to give compound **168** in 88% yield.

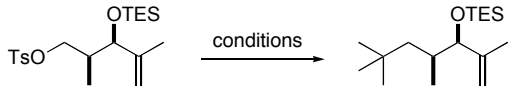


Scheme 33. Synthesis of Tosylate 95

Next we attempted the *tert*-butyl alkylation of the primary tosylate (**168**). While treatment with lithium di(*tert*-butyl)cuprate produced the coupling product in a reasonable yield on a small (0.2 g) scale, attempts to scale up the reaction were unsuccessful, yielding less than 5% of the desired product (**169**). We then investigated the use of a copper-catalyzed cross-coupling reaction of Grignard reagent (*t*-butylMgCl)

with the primary tosylate (Table 5) [69]. With the conditions reported originally (entry 3), only a 50% yield of **169** was isolated after 12 h. Increasing both the catalyst amount and reaction time resulted in a higher yield (64%) (entry 4).

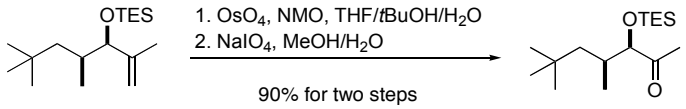
Table 5. Condition Screen for the *t*-Butyl Alkylation of 168



168 **169**

Entry	Conditions	Time (h)	Isolated Yield (%)
1	(*t*-Bu)$_2$CuLi, Et$_2$O, -20 °C **0.2 g scale**	20	47
2	(*t*-Bu)$_2$CuLi, Et$_2$O, -20 °C **2.5 g scale**	20	<5
3	*t*-BuMgCl, **2%** $CuCl_2$ **10%**, Ph—≡—Me , THF, reflux	12	50
4	*t*-BuMgCl, **10%** $CuCl_2$ **25%**, Ph—≡—Me , THF, reflux	24	64

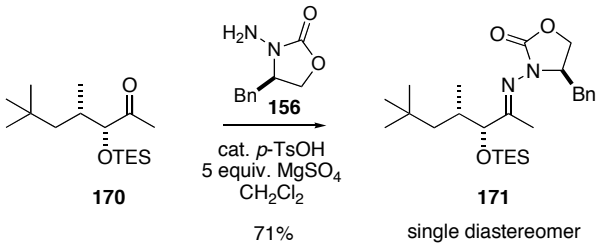
Our next step was to convert the terminal olefin to a ketone. Ozonolyis provided the ketone in somewhat low yield (approximately 40%), so we used a two-step Lemieux-Johnson oxidation, which provided the desired methyl ketone (**170**) in 90% yield (Scheme 34) [70].



169 **170**

Scheme 34. A Two-Step Procedure for Converting Terminal Olefin 169 to Ketone 170

With the desired ketone in hand, we attempted to install auxiliary **156** using the conditions we had developed with the model system. However, when we subjected ketone **170** to these conditions, no hydrazone formed. We assumed that this ketone would not form the hydrazone because its α′ side was considerably more sterically demanding in comparison to the model ketone (**170**). We rationalized that if the difference in sterics between ketone **171** and the model ketone was enough to affect its reactivity toward hydrazone formation, this bulkier ketone might also be less prone to epimerization, and thus, we could use a stronger acid. We attempted the hydrazone formation under the same conditions, but substituted *p*-TsOH for PPTS, and the hydrazone formed in 71% yield with no epimerization.

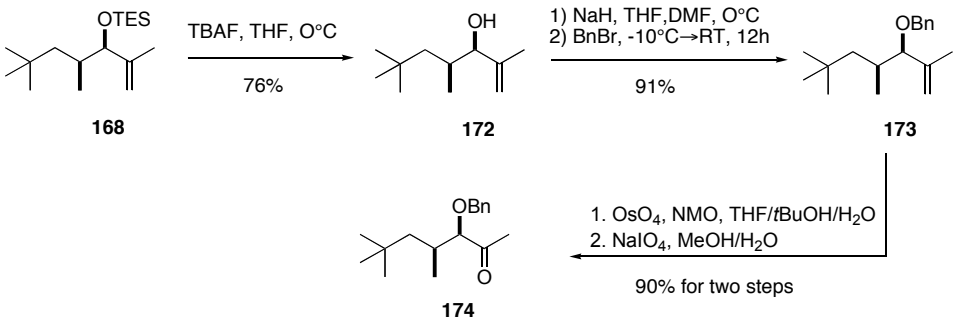


Scheme 35. Hydrazone Formation with Methyl Ketone 97

2.2.3 Bis-alkylation

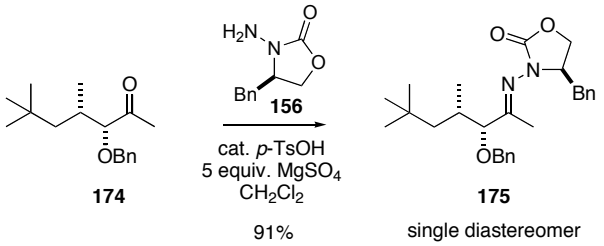
Once we had hydrazone **171** as a single diastereomer, we next investigated the subsequent α-alkylation reactions using the conditions we developed with the model system. Treatment of **171** with LDA followed by MeI afforded none of the desired product. As with hydrazone formation, we attributed this to the more sterically bulky hydrazone (**171**). Even when conducted the deprotonation at an elevated temperature (rt), we only observed 50% conversion. At this point we wanted to decrease the α′ steric

bulk of this hydrazone by switching to a smaller hydroxyl protecting group. We removed the TES protecting group in olefin **96** using TBAF and reprotected with a benzyl group to obtain compound **172**.



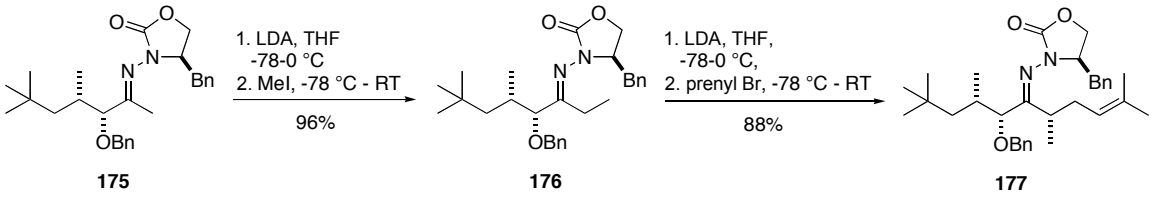
Scheme 36. Protecting Group Switching from TES to Benzyl Group

We carried out the Lemieau-Johnson oxidation as before which gave ketone **174** in 90% yield. We next had to carry out the hydrazone formation to determine to what extent the benzyl compound would epimerize. Recall that the benzyl protected model ketone (**149**) epimerized (dr = 95:5) when subjected to the conditions we developed for hydrazone formation. Since we had already established in the context of hydrazone formation that the bulkier TES protected apratoxin ketone (**170**) was less prone to epimerization in comparison to the TES protected model system, we were optimistic that the epimerization observed in the benzyl protected model system would not translate to the bulkier benzyl protected apratoxin ketone (**174**). Not only were we able to form hydrazone **175** without epimerizing the α′ stereocenter, but also the reaction yield was 91%, which was much higher than that with the corresponding TES protected ketone.



Scheme 37. Hydrazone Formation with Benzyl Protected Ketone 174

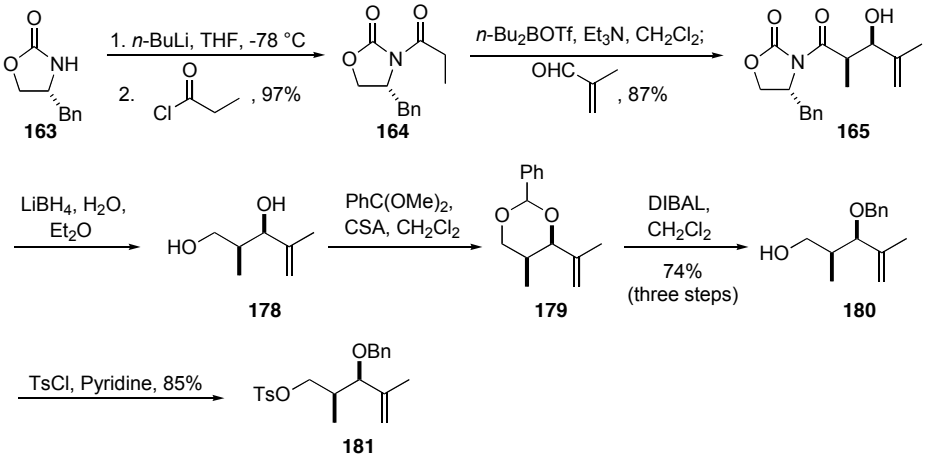
When we attempted to methylate hydrazone **175** using the same conditions developed for the model system, we observed complete conversion to the product with an isolated yield of 96%. We then prenylated the methylated hydrazone (**176**), which resulted in bisalkylated hydrazone **177** in 88% yield with a dr of 95:5, demonstrating the effectiveness of the ACC auxiliary in directing the stereoselectivity in the α-alkylation reaction. When we performed the bisalkylation in the reverse order, the dr was 84:16.



Scheme 38. Bisalkylation of Hydrazone 102

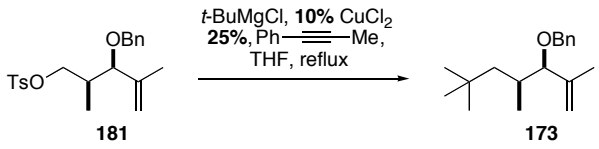
Having established that we could form the hydrazone without epimerization and perform the α,α-bisalkylation on the benzyl protected hydrazone, we wanted to incorporate the benyl protecting group early in the synthesis of ketone **174**, rather than switching protecting groups at the stage of the olefin (**168**). However, our initial attempts to install the benzyl group in acyl oxazolidinone **165** using NaH and benzyl bromide were unsuccessful. We then turned to a method for benzyl protecting the secondary alcohol of a 1,3-diol by selective ring opening of the corresponding

benzylidene acetal (**179**). The tosylation of **180** proceeded in 85% yield to give compound **181** (Scheme 39).



Scheme 39. Synthesis of Tosylate 181

Next we attempted the *tert*-butyl alkylation of the primary tosylate (**181**) using our previously established conditions (entry 4, Table 5) [69]. Gratifyingly, when we attempted this coupling on the benzyl protected tosylate, the reaction worked even better than with the TES protected tosaylate, giving 93% yield (Scheme 40). However, when this reaction was run subsequently, the yield decreased significantly (~20%). After successively replacing each reagent, we determined that the best results are obtained with new bottles of the alkyne.



Scheme 40. t-Butyl Alkylation of Tosylate 181

2.2.4 Removing the ACC Auxiliary

Several conditions exist for the deoxygenation of ketones to the corresponding alkanes. These include conversion to tosylhydrazones followed by $NaCNBH_3$ reduction[71-73], the Wolff-Kishner Reduction [74, 75], the Clemmensen Reduction [76, 77], or desulfurization with Raney nickel or a nickel borohydride [78, 79]. We ruled out the Clemmensen reduction due to the harshly acidic conditions involved. Both the Wolff-Kishner reduction and the reduction of tosylhydrazones using sodium cyanoborohydride generate a carbanion at carbonyl carbon (see Figure 4), rendering these methods incompatible with our α-hydroxy ketone due to potential elimination of the hydroxyl group.

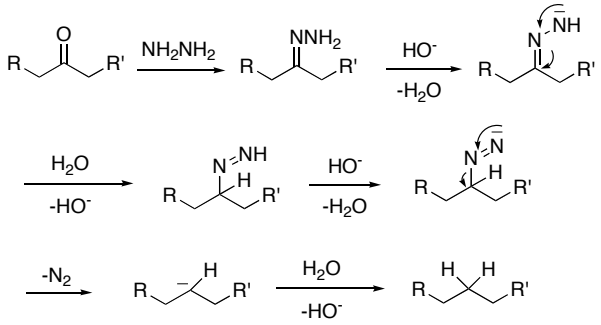
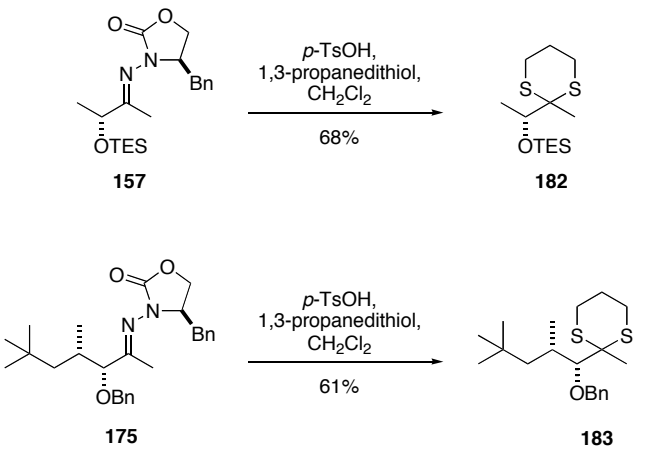


Figure 4. Wolff-Kishner Reduction

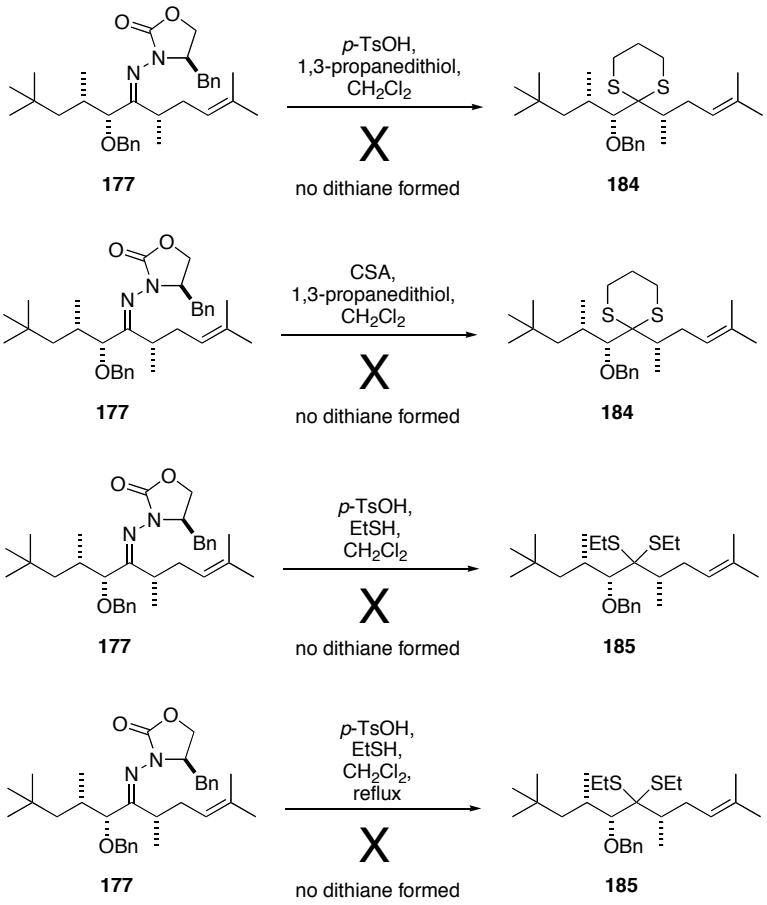
Dithiane reduction with Raney nickel could potentially work well, especially if we could form the dithiane directly from the hydrazone without first hydrolyzing to the ketone. Potentially circumventing the hydrolysis made this an attractive option because the resulting ketone would be more acidic than the hydrazone, and thus, more prone to epimerization, while the dithiane would not. The one potential limitation to this strategy is the competitive hydrogenation of alkenes, which is why we performed the second α-alkylation with prenyl bromide rather than allyl bromide, giving the more substituted olefin.

Based on a literature method [80] for converting dialkyl hydrazones directly to dithianes, we attempted to convert the non-alkylated model hydrazone (**157**) to the corresponding dithiane using 1.1 equivalent of *p*-TsOH and excess 1,3-propanedithiol. Under these conditions, we isolated the dithiane (**182**) in 68% yield as well as epimerized starting material. We then subjected our more complex apratoxin D hydrazone (**175**) to these conditions, affording dithiane **183** in 61% yield as a single diastereomer.



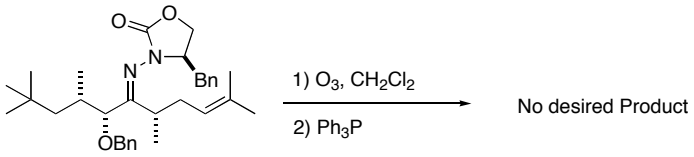
Scheme 41. Dithiane Formation from ACC Hydrazones

With this promising initial result, we attempted to form the dithiane from the bisalkylated hydrazone (**177**). We observed formation of a small amount of the epimerized ketone as well as epimerized starting material, but none of the dithiane. We tried the reaction with camphor sulfonic acid, with the same result. We then tried a smaller thiol, ethane thiol, with no change. Finally, we tried refluxing the reaction, but observed the same result. We concluded that the hydrazone was most likely too sterically hindered to undergo nucleophilic addition by the thiol.



Scheme 42. Dithiane Formation from Bisalkylated Hydrazone 177

At this stage we decided to investigate conditions to convert hydrazone **177** to the ketone (**186**), with the assumption that removing the auxiliary would decrease the steric bulk enough that the thiol could add to the carbonyl to generate the dithiane. Since the acid mediated conditions for forming the dithiane had resulted in the epimerized ketone, we started our investigation with ozonolysis, rather than acid-catalyzed hydrolysis. However, treatment of hydrazone **177** with ozone followed by reductive workup only resulted in oxidation of the double bond and no desired product.



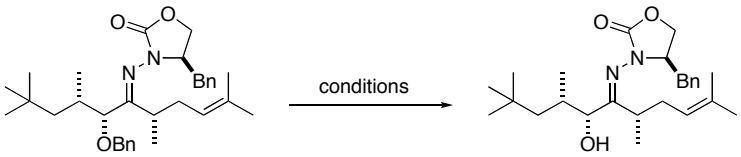
177

Scheme 43. Ozonolysis of Hydrazone 177

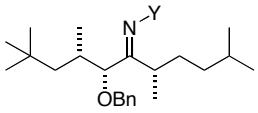
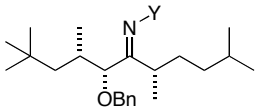
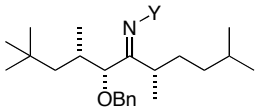
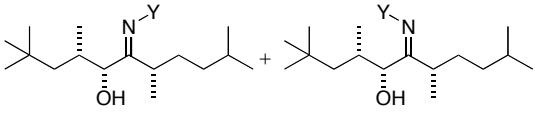
Since ozone is an electrophilic oxidant and, in contrast to a SAMP/RAMP dialkyl hydrazone, an ACC hydrazone is electron deficient, we decided to remove the protecting group from the α'-hydroxyl group in an attempt to minimize the steric bulk around the hydrazone. The standard methods for removing benzyl groups are hydrogenolysis, which would reduce the olefin, and dissolving metal reduction, which would potentially reduce the carbon-nitrogen double bond. For the immediate purpose of determining whether removing the protecting group would have an effect on auxiliary removal, we chose to remove the benzyl group via hydrogenolysis.

In an effort to remove the benyl protecting group, we carried out a standard hydrogenolysis reaction of **177** using an H_2 balloon and 10% Pd/C in EtOAC. Under these conditions the olefin was reduced to the alkane, as expected, but the benzyl group was not removed (entry 1, Table 6). We also attempted the reaction with MeOH and EtOH, but neither yielded the deprotected compound (entries 2 and 3). We then performed the reaction using 10% Pd/C and triethylsilane in MeOH (entry 4), which removed the benzyl group, reduced the olefin, and isomerized the hydrazone across the carbon-nitrogen double bond giving 65% yield of the two E/Z isomers (**188a**, **188b**). While the isomerization complicated the NMR analysis of the crude material, ultimately it did not matter, as removal of the auxiliary would converge the two isomers to a single ketone product.

Table 6. Hydrogenolysis of Hydrazone 177

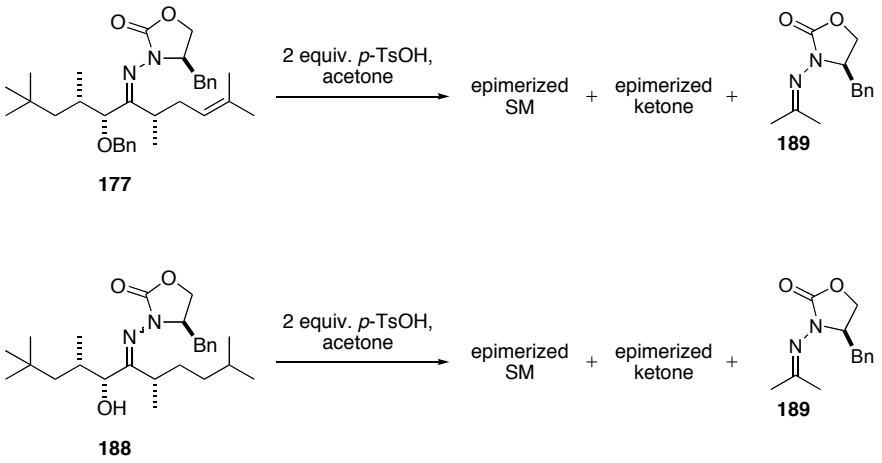


177 **186**

Entry	conditions	products
1	H_2, 10% Pd/C, EtOAc	 **187**
2	H_2, 10% Pd/C, MeOH	 **187**
3	H_2, 10% Pd/C, EtOH	 **187**
4	Et_3SiH, 10% Pd/C, MeOH	 **188a** 1:1 **188b**

At this stage we decided to investigate hydrolysis conditions starting with the conditions originally used for the ACC hydrazone method, 2 equivalents of *p*-TsOH in acetone, which rapidly hydrolyze to ketone in under 30 minutes [61]. The acid mediated conditions we used to attempt dithiane formation had resulted in the epimerized ketone, but under those conditions, the hydrazone/ketone was stirred with acid overnight. These hydrolysis conditions would potentially promote faster ketone formation, as formation of the acetone hydrazone would drive the reaction. Shorter reaction time might limit the extent of epimerization. We subjected both hydrazone **177** and hydrazone **188** to the above-mentioned conditions, and after 30 minutes for both

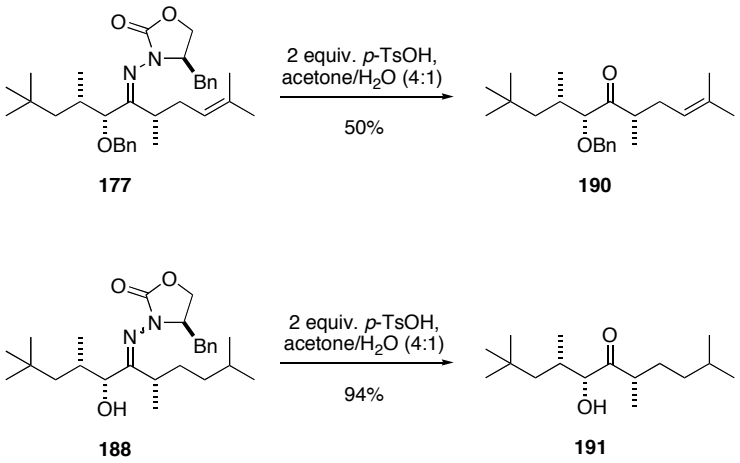
compounds we observed a mixture of the acetone hydrazone, epimerized ketone, and epimerized starting material.



Scheme 44. Attempted Hydrolysis of Compounds 177 and 188

At this point, another set of hydrolysis conditions were being investigated by another member of our group in a similarly hindered compound. Under these conditions, 2 equivalents of *p*-TsOH were still being used, but the reaction was run in a 4:1 mixture of acetone and water. The reasoning for running the reaction in a mixture of acetone and water was two-fold. By adding water to the reaction, more nucleophile would be present to drive the reaction, and the acid source would no longer be *p*-TsOH. The relatively weaker acid, H_3O^+, would be the source of protons, potentially allowing for longer reaction time without epimerization.

Hydrazone **177** was subjected to these conditions, resulting in 50% conversion to the non-epimerized ketone. When deprotected hydrazone **188** was hydrolyzed under these conditions, the ketone was isolated in 94% yield as a single diastereomer. Unfortunately, for both compounds, our initial attempts to form the dithiane failed.



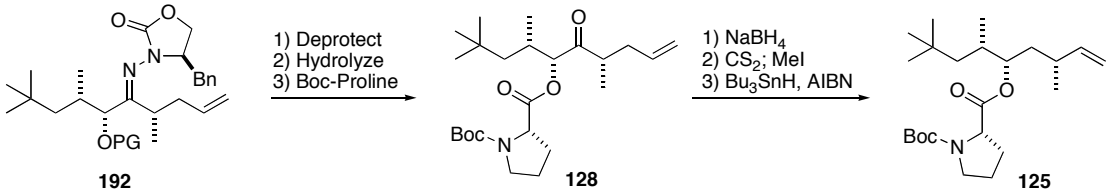
177 190 188 191

Scheme 45. Hydrolysis of Hydrazones 177 and 188

At this stage, as we were bringing more material forward, we wanted to install a different protecting group for the α'-hydroxyl group. Deprotecting hydrazone **177**, had a significant impact on the hydrolysis, but we needed to use a protecting group that could be removed without reducing the olefin. Keeping in mind that using the benzyl protecting group had improved the yield of the *t*-butyl coupling, hydrazone formation, and had been the only protecting group with which we were able to carry out the bisalkylation sequence; we chose to replace the benzyl group with a *p*-methoxy benzyl (PMB) group. The PMB group would be sterically similar to the benzyl group, but could be removed using oxidative conditions, for example DDQ, rather than hydrogenolysis.

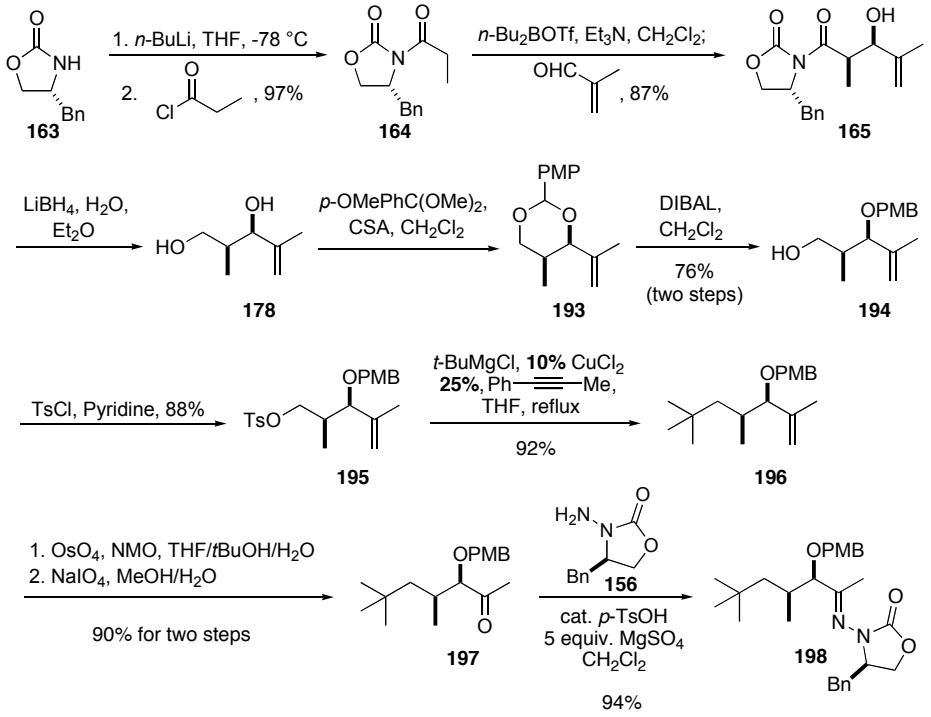
Since our initial attempts at forming the dithiane had failed, and we were somewhat concerned that the Raney nickel reduction would also reduce the olefin, we wanted to explore another deoxygenation method. We chose to investigate radical mediated deoxygenation. The Chugaev Reaction involves the sequential treatment of an alcohol with NaH followed by an excess of carbon disulfide and methyl iodide generating the xanthate. Xanthates can either undergo a *syn*-elimination to form an olefin, or upon treatment with *n*-Bu_3SnH in the presence of a radical initiator such as

AIBN, they can be used to deoxygenate an alcohol in what is known as the Barton-McCombie deoxygenation [81, 82]. By reprotecting ketone **191** as the boc-proline ester and reducing hydrolysis product **126** to the alcohol, we could employ this deoxygenation method (Scheme 46). Because the carbon-oxygen bond is cleaved homolytically, this method works well for hindered secondary alcohols and avoids the rearrangements common to carbocation reactions [82]. Another advantage to using this method is that the reaction is run under neutral conditions, and thus, epimerization should not be an issue.



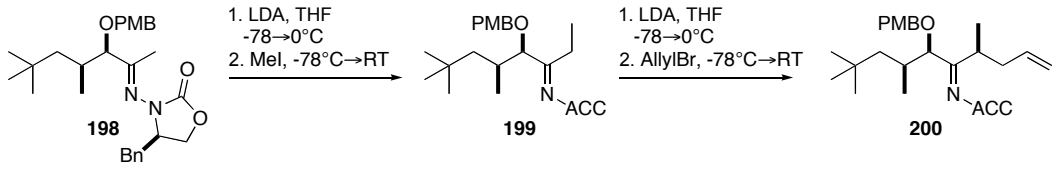
Scheme 46. Proposed Barton-McCombie Deoxygenation

Before we could explore this method for deoxygenation, we needed to advance the key apratoxin hydrazone protected as the PMB ether. We planned to do this using our original synthesis of tosylate **181**, but substituting anisaldedyde dimethyl acetal for benzaldehyde dimethyl acetal in the formation of the acetal.



Scheme 47. Synthesis of PMB Protected Hydrazone 198

This anisaldehyde acetal was opened selectively to give the free primary alcohol using DIBAL under the same conditions previously established, and the remaining steps of the synthesis were maintained giving ketone **197**. The hydrazone (**198**) was formed in 94% yield, and bisalkylated to give **200**.



Scheme 48. Bisalkylation of PMB Protected Hydrazone 198

In this case we chose to allylate the hydrazone, rather than install the prenyl group, because we wanted to suppress the radical cyclization process. The radical

cyclization would favor the 4-exo-trig product over the 5-endo-trig, and while the formation of four-membered rings is not typically favored, incorporating the allyl group would disfavor the process even more a it would lead to formation of a primary radical as apposed to the more stable tertiary radical that would form in the case where the prenyl group was present (Figure 4).

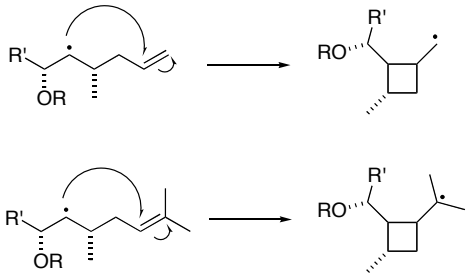
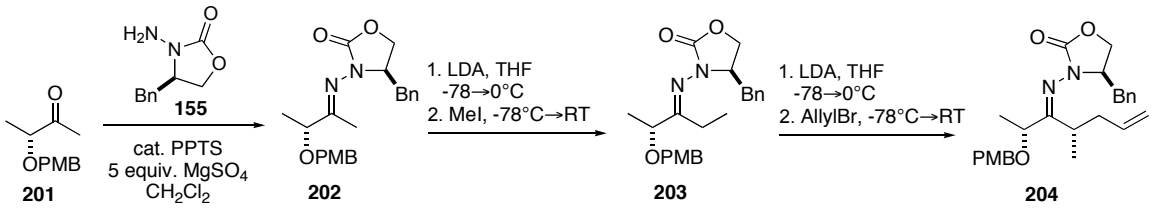


Figure 5. Potential 4-exo-trig Radical Cyclization

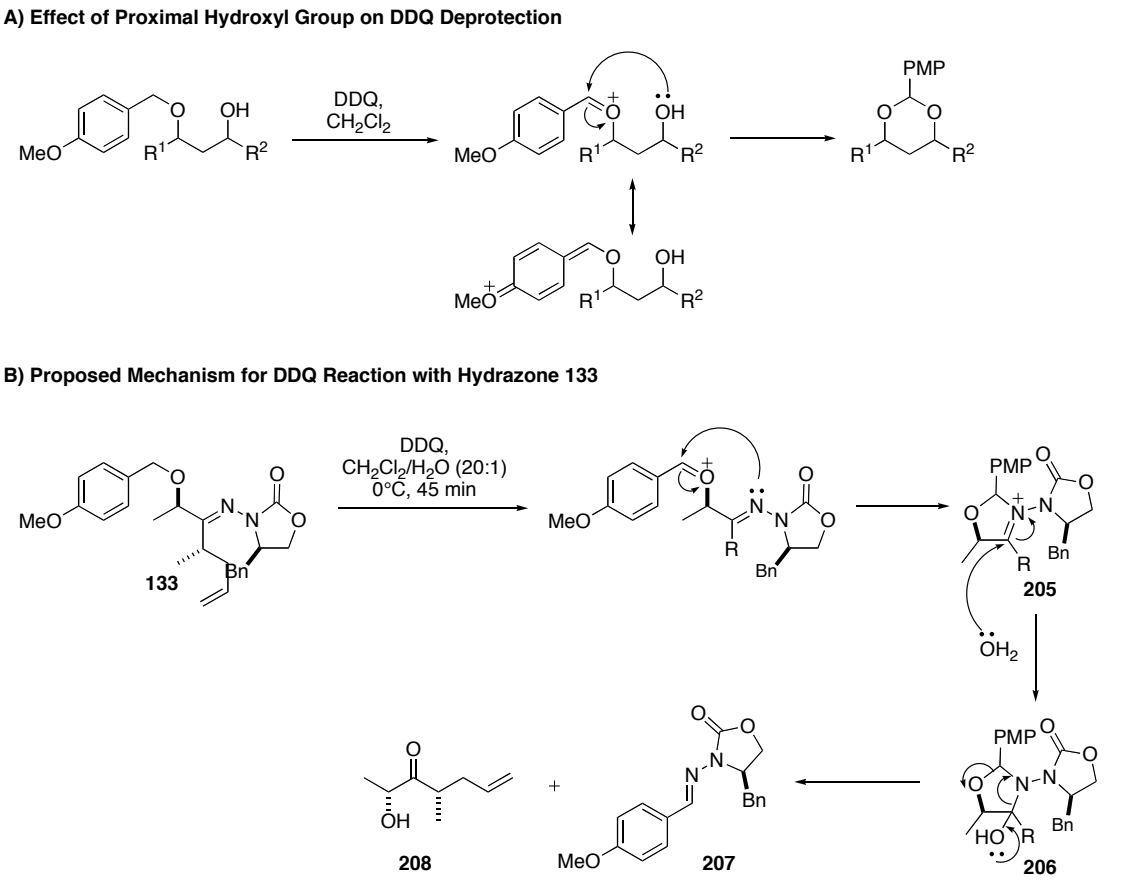
While we were generating hydrazone **198** to test this deoxygenation strategy, we also synthesized the PMB protected bisalkylated model hydrazone (**204**).



Scheme 49. Synthesis of Bisalkylated PMB Protected Hydrazone 204

We wanted to confirm that we could remove the PMB group without any side reactions. However, upon treatment with DDQ in dichloromethane/water (20:1), we did not observe formation of the deprotected hydrazone. NMR analysis of the crude material indicated that we had generated the anisaldehyde-derived hydrazone and some other minor component that we were not able to isolate. This result was confirmed

by actually carrying out this anisaldehdye-derived hydrazone formation for comparison. Upon further investigation, we found that when PMB ethers with proximal hydroxyl groups are treated with DDQ, the anisaldehyde acetals are formed [83].

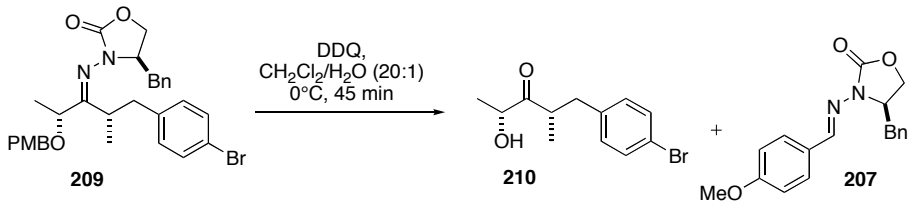


Scheme 50. DDQ Reaction

By analogy to this reaction, we proposed that the nitrogen of the hydrazone was attacking the oxonium in the same way that a proximal hydroxyl would (Scheme 50) leading to formation of compound **205**. Attack by water liberates the anisaldehyde-derived hydrazone (**207**) as well as the deprotected, hydrolyzed ketone (**208**). We most likely did not observe this ketone by NMR analysis of the crude reaction mixture because

it was volatile enough to evaporate when the reaction was concentrated under reduced pressure.

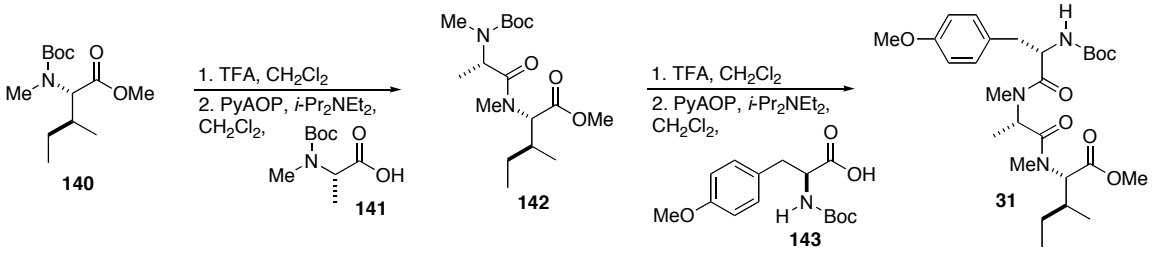
To confirm that we were in fact forming the deprotected ketone, we synthesized the higher molecular weight hydrazone **209** and repeated the reaction under the same conditions. In this case, we observed formation of the anisaldehyde-derived hydrazone (**207**) as well as the deprotected α-hydroxy ketone (**210**), thus establishing that under these conditions, we can carry out the PMB deprotection and hydrolysis to the ketone in one step.



Scheme 51. Deprotection/Hydrolysis with DDQ

2.2.5 Synthesis of Tripeptide

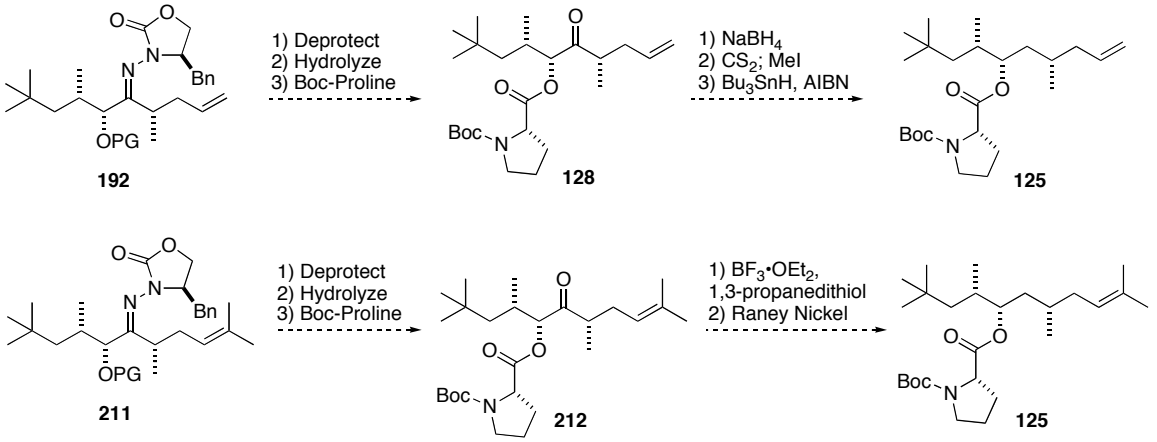
Tripeptide **31** was prepared as reported in Forsyth's synthesis of apratoxin A [48]. Assembled in a C → N fashion, isoleucine derivative **140** was deprotected and coupled with *N*-Boc, *N*-methyl-L-alanine to give compound **142**. Carbamate cleavage followed by another PyAOP-mediated condensation with *N*-Boc, *O*-methyl-tyrosine gave **31**.



Scheme 52. Synthesis of Tripeptide 31

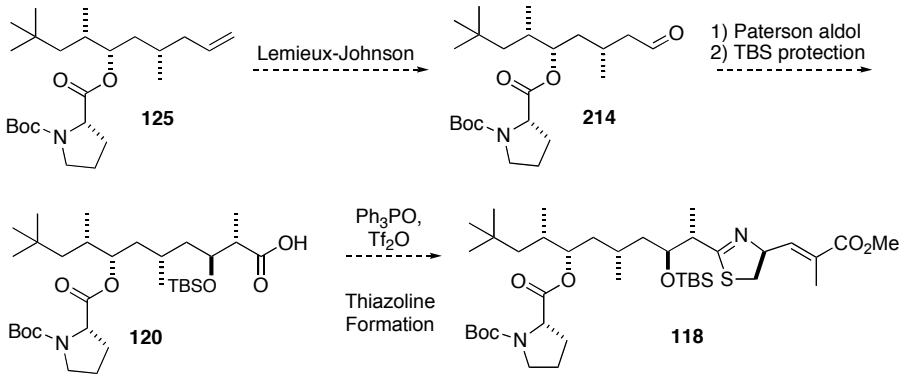
2.2.6 Future Work

At this stage we have successfully carried out the α,α-bisalkylation of compound **131** to set the C37 stereocenter. We are currently working on removal of the auxiliary and reduction to the methylene. Our immediate next step is to hydrolyze and deprotect bisalkylated hydrazone **200**. We will then reduce the methylene either by dithiane formation and Raney nickel reduction or reduction of the ketone to the alcohol followed by xanthate formation and Barton-McCombie deoxygenation .



Scheme 53. Deoxygenation

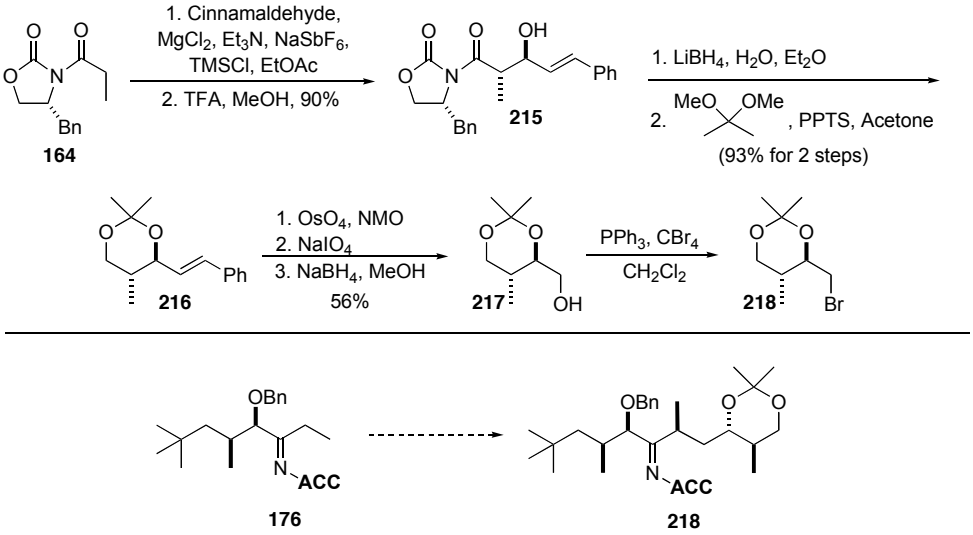
Once we have carried out the deoxygenation to obtain compound **125**, we will oxidize to the aldehyde and perform the Paterson *anti*-aldol [59] followed by thiazoline formation using the tandem deprotection/cyclodehydration strategy employed by Takahashi and Ma (Scheme 54).



Scheme 54. Future Work

Once we achieve thiazoline formation, we just have to couple compound **118** with the tripeptide (**54**), carry out the macrolactamization, and perform the TBS deprotection.

In addition to these short-term next steps, we would also like to ultimately perform the bisalkylation using an advanced alklylating agent that would already contain the C34 and C35 stereocenters. This alklylating agent has been synthesized, but the transformation has yet to be attempted.



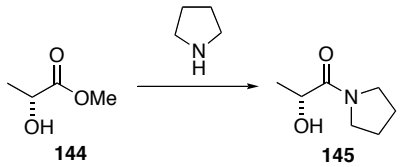
Scheme 55. Synthesis of Advanced Alkylating Agent

2.3 Conclusion

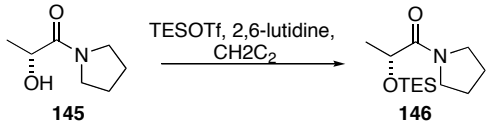
In conclusion, we have demonstrated the utility of the ACC hydrazone method for the key step in the synthesis of apratoxin D. We were able to install the auxiliary in an advanced ketone intermediate without epimerizing an existing α′-stereocenter. We then successfully performed the α,α-bisalkylation in the advanced intermediate setting the C37 stereochemistry with high stereoselectivity, indicating the existing α′-stereocenter had little to no effect of the selectivity of the ACC alkylation. This result is notable as it demonstrates that this method can be used in both early and late stages of a total synthesis, the latter scenario being relatively less common in the asymmetric total synthesis of natural products. While the compound generated by the bisalkylation was quite sterically hindered, we were able to develop epimerization-free conditions for hydrolysis to the ketone. In addition, we discovered a very interesting reaction with DDQ, which effects the deprotection and hydrolysis of OPMB-protected α-hydroxy hydrazone **209** in one step.

2.4 Experimental

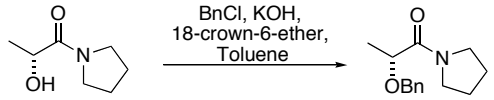
General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et_2O, CH_2Cl_2, THF, MeCN, and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et_3N, pyridine, *i*-Pr_2NEt, 2,6-lutidine, *i*-Pr_2NH, and TMEDA were distilled from CaH_2 under a N_2 atmosphere prior to use. Brine (NaCl), $NaHCO_3$, and NH_4Cl refer to saturated aqueous solutions. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR were recorded on a Varian INOVA 400 MHz spectrometer at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS; ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). MS data were collected from Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was performed on a 4.6 X 250 nm Chiralcel OD-H column (Chiral Technologies).



***N*-[(*R*)-propanoyl]pyrrolidine (145).** Pyrrolidine (1.9 mL, 23.0 mmol) was added to a round-bottom flask containing (+)-methyl-D-lactate (2 mL, 20.9 mmol). The mixture was stirred at rt for 24 h and evaporated under reduced pressure. The crude material was used without further purification in the next step.

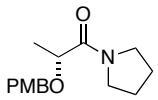


***N*-[(*R*)-2-triethylsilyoloxypropanoyl]pyrrolidine (146).** Et_3N (6.7 mL, 48.1 mmol) and DMAP (~0.11 g) were added to a cooled (ice-H_2O bath), stirred solution of the crude amide **145** from above (2.75 g, 19.2 mmol) in CH_2Cl_2 (24 mL). TESCl (4.8 mL, 28.9 mmol) was added dropwise. Stirring was continued 10 min, the cooling bath was removed and stirring was continued for 16 h. The reaction was diluted with Et_2O (30 mL), and washed successively with 1 M HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 70:30 EtOAc-Hexane gave **146** (4.80 g, 97%) as a pure, clear oil. Characterization data matched that reported in the literature [66].



145 147

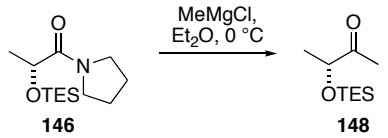
***N*-[(*R*)-2-benzyloxypropanoyl]pyrrolidine (147).** KOH (3.27 g, 58.3 mmol) was added to a cooled (ice-H_2O bath) and stirred solution of crude **145** from above (2.78 g, 19.4 mmol), benzyl bromide (3.47 mL, 29.2 mmol), and 18-crown-6-ether (0.26 g, 0.972 mmol) in toluene (50 mL). Stirring was continued for 16 h. The reaction was quenched with H_2O (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 80:20 EtOAc/Hexane gave **147** (3.89 g, 86%) as a pure, clear oil. Characterization data matched that reported in the literature [66].



219

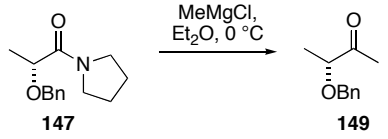
***N*-[(*R*)-2-(4-bromo)-benzyloxypropanoyl]pyrrolidine (219).** KOH (1.05 g, 18.7 mmol) was added to a stirred and cooled (ice-H_2O bath) solution of crude XX from above (0.9 g, 6.24 mmol), *p*-Bromobenzyl chloride (1.3 mL, 9.36 mmol), and 18-crown-6-ether (0.08 g, 0.312 mmol) in toluene (20 mL). Stirring was continued 16 h. The reaction was quenched with H_2O (15 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 80:20 EtOAc/Hexane gave **219** (1.48 g, 90%) as a pure, clear oil. Characterization data matched that reported in the literature [66].

The following reaction is representative of those depicted in Scheme 30:



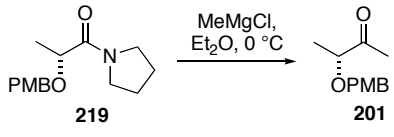
146 **148**

(*R*)-3-triethylsilyloxy-2-butanone (148). Methyl magnesium bromide (5.2 mL of a 1 M solution in Et_2O, 15.5 mmol) was added dropwise over ca. 10 min. to a stirred and cooled (ice-H_2O bath) solution of amide **146** from above (1.0 g, 3.88 mmol) in Et_2O (48 mL). Stirring was continued for 2 h and the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The organic layer was separated and washed with saturated aqueous NH_4Cl (15 mL) and H_2O (15 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave **148** (0.68 g, 87%) as a pure, clear oil. Characterization data matched that reported in the literature [66].



147 **149**

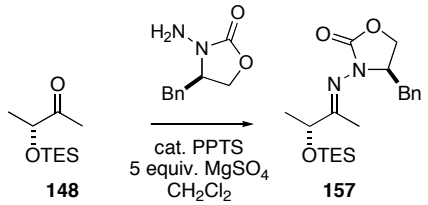
(*R*)-3-benzyloxy-2-butanone (148). Flash chromatography over silica gel, using 15:85 EtOAc/Hexane gave **149** (0.84 g, 88%) as a pure, colorless oil. Characterization data matched that reported in the literature [66].



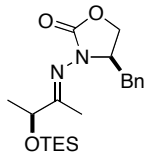
219 **201**

(*R*)-3-(4-methoxy)-benzyloxy-2-butanone (201). Flash chromatography over silica gel, using 15:85 EtOAc/Hexane gave **201** (0.67 g, 91%) as a pure, colorless oil. Characterization data matched that reported in the literature [66].

The following reaction is representative of those depicted in Schemes 31:

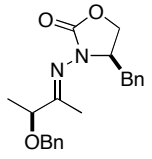


ACC Hydrazone 157. ACC auxiliary **156** (0.41 g, 1.63mmol) was added to a stirred solution of ketone **148** (0.30g, 1.48 mmol) and $MgSO_4$ (0.89g, 7.40 mmol) in CH_2Cl_2 (15 ml). PPTS (0.02g, 0.074 mmol) was added and stirring was continued 24h. The mixture was filtered, diluted with diethyl ether (20 ml), and washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave **157** (0.51 g, 91%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.16–7.37 (m, 5H), 4.55 (q, *J* = 8.0 Hz, 1H), 4.28-4.24 (m, 2H), 4.06-4.10 (m, 1H), 3.16-3.21 (m, 1H), 2.72-2.78 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.0 (s, 3H), 1.34 (d, *J* = 8.0 Hz, 3H), 0.89 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H). **HPLC** (Daicel Chiralcel OD-H, hexane—*i*-prOH = 1/99, flow rate 0.5 mL/min, λ = 210 nm): t_R 18.6 min (major diastereomer), 14.9 min (minor diastereomer). major: minor = 99.5:0.5.



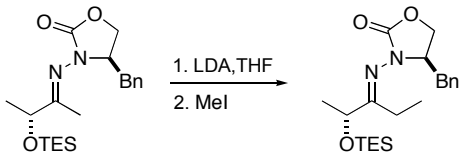
158

Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave **158** (0.18 g, 89%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18–7.38 (m, 5H), 4.53 (q, *J* = 6.0 Hz, 1H), 4.31-4.39 (m, 1H), 4.24 (app. t, *J* = 8.0 Hz, 1H), 4.02 (dd, *J* = 8.0, 10.6 Hz, 1H), 3.14 (dd, *J* = 3.4, 13.1, Hz, 1H), 2.70 (dd, *J* = 8.0 Hz, 13.1 Hz, 1H), 2.01 (s, 3H), 1.37 (d, *J* = 8.0 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H). **HPLC** (Daicel Chiralcel OD-H, hexane—*i*-prOH = 99/1 , flow rate 0.5 mL/min, λ = 210 nm): t_R 14.1 min (major diastereomer), 17.8 min (minor diastereomer). major: minor = 99.5:0.5.



220

Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave **220** (0.23 g, 90%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.17–7.37 (m, 10H), 4.40-4.49 (m, 3H), 4.36 (app. t, J = 8.6 Hz, 1H), 4.25 (q, J = 5.7 Hz, 1H), 4.05 (app. t, J = 8.6 Hz, 1H), 3.15 (dd, J = 5.7, 14.3 Hz, 1H), 2.75 (dd, J = 8.5, 14.3 Hz, 1H), 2.06 (s, 3H), 1.42 (d, J = 5.7 Hz, 3H). **HPLC** (Daicel Chiralcel OD-H, hexane-*i*-prOH = 99/1 , flow rate 0.5 mL/min, λ = 210 nm): t_R 10.8 min (major diastereomer), 22.3 min (minor diastereomer). major-minor = 95.4:4.6.

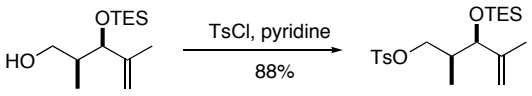


157 **159**

Methylated ACC Hydrazone 159. *n*-BuLi (2.5 M in hexanes, 0.32 mL, 0.797 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.12 mL, 0.85 mmol) in THF (3 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **157** (0.10 g, 0.266 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transfered to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, methyl iodide (0.33 mL, 5.31 mmol) was added and stirring was continued for 5 min. The cold bath was removed and stirring was continued for an additional 1h and then the reaction mixture was partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **159** (0.0998 g, 96%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18-7.27 (m, 5H), 4.57 (q, *J* = 8.0 Hz, 1H), 4.30-4.20 (m, 2H), 4.08-4.02 (m, 1H), 3.18 (dd, *J* = 4.0, 8.0 Hz), 2.42-2.74 (m, 3H), 1.39 (d, *J* = 8.0 Hz, 3H), 1.18 (t, *J* = 8.0 Hz, 3H), 0.98 (t, *J* = 12.0 Hz, 9H), 0.65 (q, *J* = 12.0, 6H).

159 **160**

Allylated ACC Hydrazone 160. *n*-BuLi (2.5 M in hexanes, 0.172 mL, 0.43 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.062 mL, 0.443 mmol) in THF (3 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **159** (0.056 g, 0.143 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, allyl bromide (0.050 mL, 0.572 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **160** (0.061 g, 93%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18-7.30 (m, 5H), 5.68-5.78 (m, 1H), 4.90-5.11(m, 2H), 4. 73 (q, *J* = 6.4 Hz, 1H), 4.28-4.37 (m, 1H), 4.22 (app. t, *J* = 8.0, 1H), 4.03 (app. t, *J* = 8.0 Hz, 1H), 3.12-3.22 (m, 2H), 2.62 (dd, *J*=6.4, 12 Hz, 1H), 2.37-2.45 (m, 1H), 2.21-2.28 (m, 1H), 1.45 (d, *J* = 8.0 Hz, 3H) 1.25 (d, *J* = 8.0 Hz, 3H), 1.0 (t, *J* = 8.0, 9H), 0.68 (q, *J* = 8.0 Hz, 6H).

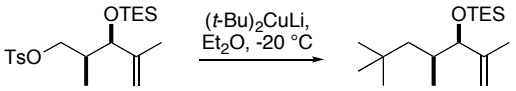


167 **168**

(2*S*,3*R*)-2,4-Dimethyl-3-(triethylsilyloxy)pent-4-enyl 4-methylbenzenesulfonate (168). *p*-Toluenesulfonyl chloride (0.137 g, 0.72 mmol) was added to a stirred solution of (2S,3R)-2,4-dimethyl-3-(triethylsilyloxy)pent-4-en-1-ol (**167**) (0.147 g , 0.6

mmol) in neat pyridine (2.0 mL). Stirring was continued for 12 h and the mixture was quickly poured into a mixture of H_2O and ice (30 mL), extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% (v/v) aqueous HCl (20 mL) and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **168** (0.211 g; 88%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.87–4.85 (m, 1H), 4.82–4.80 (m, 1H), 3.97 (d, *J* = 6.0 Hz, 1H), 3.94 (A of an ABX system, apparent dd, *J* = 6.0, 9.6 Hz, 1H), 3.82 (B of an ABX system, apparent dd, *J* = 6.0, 9.6 Hz, 1H), 2.45 (s, 3H), 1.96–1.85 (X of an ABX system, m, 1H), 1.59 (s, 3H), 0.90 (apparent t, *J* = 8.0 Hz, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.57-0.48 (m, 6H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 145.3, 144.8, 133.2, 129.9, 128.0, 112.5, 76.0, 72.9, 36.7, 21.7, 18.1, 11.3, 6.9, 4.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{34}NaO_4SSi$: 421.2, found: 421.1.

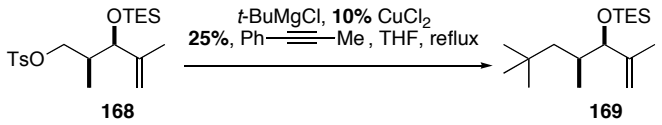
The following reactions are representatives of those depicted in Table 5:



168 **169**

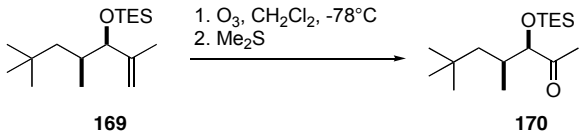
Triethyl((3R,4S)-2,4,6,6-tetramethylhept-1-en-3-yloxy)silane (169). *t*BuLi (2.9 mL, 5.0 mmol, 1.7 M in pentane) was added to a suspension of CuI (0.476 g, 2.5 mmol) in Et_2O (3.0 mL) at –40 °C. Stirring was continued for 30 min at –40 °C and the mixture was then transferred to a –20 °C bath. A solution of **168** (0.199 g, 0.5 mmol) in Et_2O (1.5 mL) was slowly added to the cuprate solution over ca. 30 min. Stirring was continued for 20 h and then allowed to warm to 0 °C. Saturated aqueous NH_4Cl was added and stirring was continued for 10 min. The mixture was allowed to warm to rt

and the mixture was partitioned between EtOAc (30 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a light-yellow oil. Flash chromatography over silica gel, using neat hexane gave **237** (0.067 g; 47%) as a pure, colorless oil and recovered **235** (0.050 g; 41%), of which spectroscopic data was identical to that reported previously. For compound **169**: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.87–4.85 (m, 1H), 4.84–4.82 (m, 1H), 3.72 (d, *J* = 6.4 Hz, 1H), 1.67 (s, 3H), 1.64–1.54 (X of an ABX system, m, 1H), 1.35 (A of an ABX system, apparent dd, *J* = 2.4, 14.0 Hz, 1H), 0.98–0.90 [13H, contains a m (B of an ABX system, 1H), a d (*J* = 6.8 Hz, 3H), and an apparent t (*J* = 8.0 Hz, 9H)], 0.88 (s, 9H), 0.59 (apparent q, *J* = 8.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 146.9, 112.3, 82.2, 47.5, 33.3, 31.1, 30.3, 18.3, 17.8, 7.1, 5.1; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{36}NaOSi$: 307.2, found: 307.2.



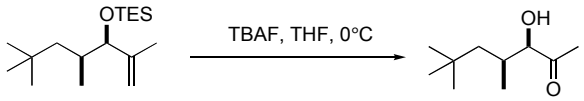
Triethyl((3R,4S)-2,4,6,6-tetramethylhept-1-en-3-yloxy)silane (169). *t*-BuMgCl (5.0 mL, 5.0 mmol, 1.0 M in THF) was added to a stirred solution of **168** (1.0 g, 2.5 mmol), $CuCl_2$ (0.034 g, 0.25 mmol) and 1-phenyl-1-propyne (78 μL, 0.625 mmol) in THF (25 mL). The reaction mixture was heated to reflux for 24 h and then allowed to cool to rt. Saturated aqueous NH_4Cl (25 mL) was added and stirring was continued for 10 min. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced

pressure to give a light-yellow oil. Flash chromatography over silica gel, using neat hexane gave **169** (0.456 g; 64%) as a pure, colorless oil. Spectroscopic data was identical to that reported above.



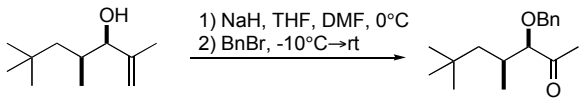
169 **170**

(3R,4S)-4,6,6-Trimethyl-3-(triethylsilyloxy)heptan-2-one (169). O_3 was bubbled through a stirred and cooled (–78 °C) solution of **168** (0.882 g, 3.1 mmol) in CH_2Cl_2 (50 mL) until a blue coloration appeared. Air was then bubbled through the solution for an additional 20 min. Me_2S (2.28 mL, 31 mmol) was added to the reaction mixture at, stirring was continued for 12 h, and the mixture was allowed to warm to rt. The mixture was partitioned between EtOAc (100 mL) and H_2O (30 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a light-yellow oil. Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave **169** (0.338 g; 38%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.79 (d, J = 5.2 Hz, 1H), 2.15 (s, 3H), 1.90–1.80 (X of an ABX system, m, 1H), 1.40 (A of an ABX system, apparent dd, J = 2.8, 14.4 Hz, 1H), 1.00–0.92 [13H, contains a m (B of an ABX system, 1H), a d (J = 6.8 Hz, 3H), and an apparent t (J = 8.0 Hz, 9H)], 0.90 (s, 9H) 0.62 (apparent q, J = 8.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 212.2, 84.1, 46.5, 34.1, 31.1, 30.0, 26.3, 17.5, 6.9, 5.0 ; **ESI-MS** m/z $[M + Na]^+$ calcd for $C_{16}H_{34}NaO_2Si$: 309.2, found: 309.2.



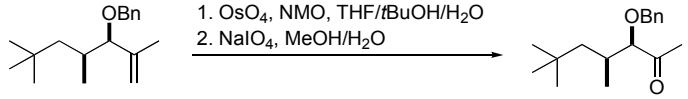
169 **172**

(3*R*,4*S*)-2,4,6,6-Tetramethylhept-1-en-3-ol (172). TBAF (2.5 mL, 2.5 mmol, 1.0 M in THF) was added dropwise to a stirred and cooled (ice-H_2O bath) solution of **168** (0.356 g, 1.25 mmol) in THF (20 mL). Stirring was continued for 2 h, saturated aqueous $NaHCO_3$ (5 mL) was then added, stirring was continued for 5 min, and the mixture was allowed to warm to rt. The mixture was partitioned between EtOAc (50 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **170** (0.162 g; 76%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.97–4.95 (m, 1H), 4.91–4.89 (m, 1H), 3.89–3.84 (m, 1H), 1.71 (s, 3H), 1.56–1.52 (X of an ABX system, m, 1H), 1.45 (A of an ABX system, apparent dd, J = 3.2, 14.0 Hz, 1H), 1.08 (B of an ABX system, apparent dd, J = 6.8, 14.0 Hz, 1H), 0.92 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 146.8, 111.2, 80.5, 47.9, 31.9, 31.2, 30.1, 19.1, 15.9; **ESI-MS** m/z $[M + Na]^+$ calcd for $C_{11}H_{22}NaO$: 193.2, found: 193.2.



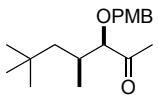
172 **173**

(((3R,4S)-2,4,6,6-Tetramethylhept-1-en-3-yloxy)methyl)benzene (173). A solution of **172** (0.255 g, 1.5 mmol) in THF (3.0 mL) was added dropwise via cannula to a stirred and cooled (ice-H_2O bath) suspension of NaH (0.108 g, 4.5 mmol) in DMF (3.0 mL). Stirring was continued for 15 min, the mixture was then cooled to -10 °C and benzyl bromide (0.27 mL, 2.25 mmol) was added. Stirring was continued for 1 h and the mixture was allowed to slowly warm to rt, and then stirred an additional 12 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, stirring was continued for 5 min, and the mixture was partitioned between EtOAc (30 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **173** (0.355 g; 91%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40–7.22 (m, 5H), 5.06–5.02 (m, 1H), 4.95–4.88 (m, 1H), 4.52 and 4.22 (AB q, $\Delta\nu_{AB}$ = 121.0 Hz, J = 12.0, 121.0 Hz, 2H), 3.34 (d, J = 7.6 Hz, 1H), 1.77–1.61 [4H, contains a s (1.69, 3H) and a m (X of an ABX system, 1H)], 1.33 (A of an ABX system, apparent dd, J = 2.0, 14.0 Hz, 1H), 1.03 (d, J = 6.4 Hz, 3H), 0.92 (B of an ABX system J = 8.0, 14.0 Hz, 1H), 0.87 (s, 9H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 143.6, 139.2, 128.4, 128.0, 127.4, 114.9, 88.8, 70.6, 47.2, 32.0, 31.0, 30.3, 18.7, 17.8; **ESI-MS** m/z $[M + Na]^+$ calcd for $C_{18}H_{28}NaO$: 283.2, found: 283.2.



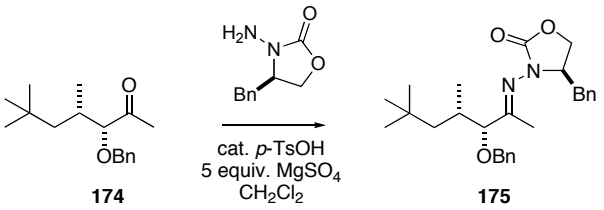
173 **174**

(3R,4S)-3-(Benzyloxy)-4,6,6-trimethylheptan-2-one (174). NMO (0.129 g, 1.10 mmol) and OsO_4 (0.31 mL, 0.025 mmol, 2.5 wt% in *t*-BuOH) were added to a stirred solution of **173** (0.143 g, 0.55 mmol) in THF (2.0 mL), *t*-BuOH (2.0 mL) and H_2O (0.5 mL). The mixture was vigorously stirred for 16 h, and then Na_2SO_3 (0.25 g) was added, followed by H_2O (3.0 mL). Stirring was continued for 30 min. The mixture was partitioned between EtOAc (20 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil. The crude material was dissolved in a mixture of MeOH (4.0 mL) and H_2O (2.0 mL) and then cooled (ice-H_2O bath). $NaIO_4$ (0.235 g, 1.10 mmol) was added portionwise, the mixture was allowed to warm to rt, and stirring was continued for 3 h. The mixture was partitioned between EtOAc (20 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **174** (0.128 g; 90%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40–7.26 (m, 5H), 4.62 and 4.37 (AB q, $\Delta\nu_{AB}$ = 101.6 Hz, J = 11.6, 101.6 Hz, 2H), 3.56 (d, J = 5.2 Hz, 1H), 2.17 (s, 3H) 2.02–1.88 (X of an ABX system, m, 1H), 1.36 (A of an ABX system, apparent dd, J = 3.2, 14.4 Hz, 1H), 1.06 (B of an ABX system, apparent dd, J = 6.8, 14.4 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 211.6, 137.7, 128.5, 128.0, 127.9, 90.0, 73.0, 46.8, 32.5, 31.0, 29.9, 26.6, 17.9; **ESI-MS** m/z $[M + Na]^+$ calcd for $C_{17}H_{26}NaO_2$: 285.2, found: 285.2.



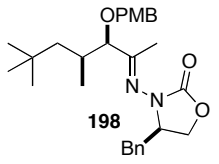
197

Ketone 197. Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **197** (0.128 g; 90%) as a pure, colorless oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.91–7.25 (m, 4H), 4.55, 4.30 (ABq, J_{AB} = 12.0 Hz, 2H), 3.81 (s, 3H), 3.50 (d, J = 5.0 Hz, 1H), 2.18 (s, 3H) 1.91 (m, 1H), 1.35 (m, 1H), 1.05 (m, 1H), 0.95 (d, J = 8.0 Hz, 3H), 0.82 (s, 9H).



174 175

ACC Hydrazone 175. ACC auxiliary **156** (0.19 g, 0.974 mmol) was added to a stirred solution of ketone **174** (0.17g, 0.649 mmol) and $MgSO_4$ (0.39g, 3.25 mmol) in CH_2Cl_2 (15 ml). *p*-TsOH·H_2O (0.012g, 0.065 mmol) was added and stirring was continued 24h. The reaction was filtered, diluted with Et_2O (20 ml), and washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 15:90 EtOAc-Hexane gave **175** (0.219g, 78%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18–7.40 (m, 10H), 4.68, 4.38 (ABq, J_{AB} = 12.0, 2H) 4.36-4.44 (m, 1H), 4.26 (app. t, J = 10.0, 1H), 4.08 (app. t, J = 10.0, 1H), 3.66 (d, J = 8.0, 1H), 3.19 (dd, J = 4.0, 16.0 Hz, 1H), 2.73 (dd, J = 6.0, 16.0 Hz, 1H), 2.05 (s, 3H), 1.87-1.94 (m, 1H), 1.37-1.42 (m, 1H), 1.14 (d, J = 4.0, 3H), 1.03-1.10 (m, 1H), 0.87 (s, 9H).



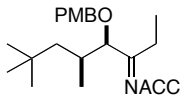
198

ACC Hydrazone 198. Flash chromatography over silica gel, using 20:80 EtOAc-Hexane gave **198** (0.354g, 78%) as a clear oil: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.85-7.31 (m, 9H), 4.61(d, *J* = 12.0 Hz, 1H), 4.36-4.44 (m, 1H), 4.24-4.34 (m, 2H), 4.08 (app, t, *J* = 9.3, 1H), 3.81 (s, 3H), 3.64 (d, *J* = 8.0 Hz, 1H), 3.16-3.21 (m, 1H), 2.72 (dd, *J* = 9.0, 13.0 Hz, 1H), 2.04 (s, 3H), 1.35 (m, 1H), 1.84-1.92 (m, 1H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.02-1.08 (m, 1H), 0.90 (s, 9H).

175 **176**

Methylated ACC Hydrazone 176. *n*-BuLi (2.5 M in hexanes, 0.70 mL, 1.76 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.26 mL, 1.82 mmol) in THF (1.5 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **175** (0.256 g, 0.587 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, methyl iodide (0.73 mL, 11.73 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **176** (0.254g, 96%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.19-7.42 (m, 10H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.20-4.41 (m, 1H), 4.36 (d, *J* = 12.0 Hz, 1H),

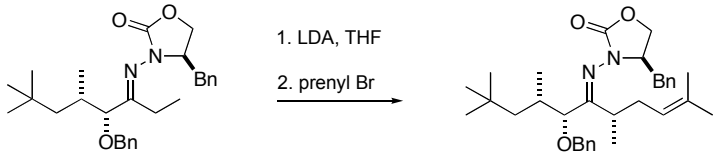
4.29 (app t., J = 8.0 Hz, 1H), 4.90 (app t., J = 8.0 Hz, 1H), 3.99 (d, J = 4.8 Hz, 1H), 3.21 (dd, J =4.0, 13.3 Hz, 1H), 2.76 (dd, J = 9.3, 13.3 Hz, 1H), 2.62-2.71 (m, 1H), 2.31-2.41 (m, 1H), 1.95-2.03 (m, 1H), 1.39-1.49 (m, 1H), 1.28 (t, J = 8.0 Hz, 3H), 1.13-1.16 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 9.01 (s, 9H).



199

Methylated ACC Hydrazone 199. *n*-BuLi (2.5 M in hexanes, 0.257 mL, 0.642 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.092 mL, 0.663 mmol) in THF (1 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **198** (0.10 g, 0.214 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, methyl iodide (0.27 mL, 4.29 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **199** (0.254g, 96%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.85-7.35 (m, 9H), 4.68 (d, J = 10.6 Hz, 1H), 4.38-4.47 (m, 1H), 4.24-4.31 (m, 2H), 4.07 (app. t., J = 9.3 Hz, 1H), 3.84 (d, J = 5.6 Hz, 1H), 3.79, (s, 3H), 3.16-3.22 (m, 1H), 2.71-2.80 (m, 1H), 2.59-2.68 (m, 1H), 2.28-2.39 (m, 1H), 1.90-1.98 (m, 1H), 1.38-1.45

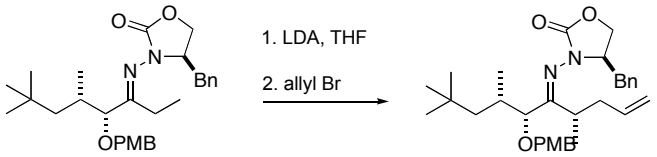
(m, 1H), 1.16 (t, J = 8.0 Hz, 3H), 1.10-1.15 (m, 1H) 1.09 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H).



176 **177**

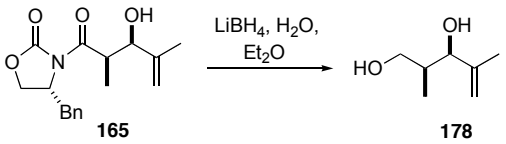
Methylated ACC Hydrazone 177. *n*-BuLi (2.5 M in hexanes, 0.56 mL, 1.41 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.204 mL, 1.46 mmol) in THF (1 mL) (Ar atmosphere). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **176** (0.22 g, 0.47 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture transferred to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, prenyl bromide (0.27 mL, 4.29 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **177** (0.215g, 88%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.10-7.41 (m, 10H), 5.10 (m, 1H), 4.70, 4.33 (ABq, J_{AB} = 12.0 Hz, 2H), 4.42-4.51 (m, 1H), 4.23 (app. t., J = 8.0 Hz, 1H), 4.13 (d, J = 2.0 Hz, 1H), 4.04 (app. t., J = 11.2 Hz, 1H), 3.16-3.26 (m, 2 H), 2.64 (dd, J = 10.6, 13.3, Hz, 1H), 2.04-2.24 (m, 3H), 1.70 (s, 3H), 1.63 (s, 1H), 1.49-1.54 (m, 1H), 1.25 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.91, (s, 9H). **HPLC** (Daicel Chiralcel OD-H, hexane-*i*-

prOH = 99/1 , flow rate 0.5 mL/min, λ = 210 nm): t_R 21.7 min (major diastereomer), 9.97 min (minor diastereomer). major-minor = 95.6:4.4.



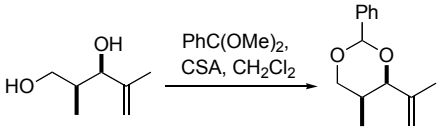
199 **200**

Methylated ACC Hydrazone 200. *n*-BuLi (2.5 M in hexanes, 0.155 mL, 0.387 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.056 mL, 0.40 mmol) in THF (1 mL). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **199** (0.062 g, 0.129 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture transferred to an ice-H_2O bath and stirred for 1h. The solution was cooled to –78 °C, allyl bromide (0.045 mL, 0.516 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **200** (0.058g, 86%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.85-7.30 (m, 9H), 5.67-5.80 (m, 1H), 5.03-5.14 (m, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.42-4.49 (m, 1H), 4.20-4.31 (m, 2H), 4.32 (d, *J* = 4.0 Hz, 1H), 4.12-4.19 (m, 1H), 3.80 (s, 3H), 3.24-3.18 (m, 2H), 2.66 (dd, *J* = 9.6, 12.8 Hz, 1H), 2.31-2.38 (m, 1H), 2.06-2.21 (m, 2H), 1.48-1.51 (m, 1H), 1.24 (d, *J* = 13.0 Hz, 3H), 1.07 (d, *J* = 12.0 Hz, 3H), 0.90 (s, 9H).



165 178

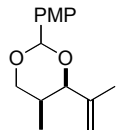
Diol 178. $LiBH_4$ (4.52 ml, 9.04 mmol) was added dropwise to a stirred, cooled (ice-H_2O bath) solution of compound **165** (2.49g, 8.22 mmol) and H_2O (0.16 ml, 9.04 mmol) in diethyl ether (30 ml). Stirring was continued 5h at rt. The mixture was cooled using an ice-H_2O bath and quenched with 1 M NaOH (20 mL). Stirring was continued 10 min, and the mixture was poured into water (15 mL). The aqueous layer was extracted with diethyl ether (3 x 20 ml). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was used without purification in the next step.



178 179

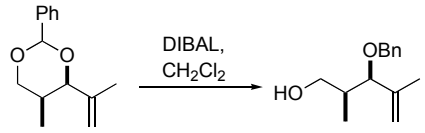
Benzylidene Acetal 179. Benzaldehyde dimethyl acetal (1.2 ml, 7.94 mmol) was added to a stirred solution of crude diol **178** from above above (7.39) mmol in CH_2Cl_2 (25 ml). Camphor sulfonic acid (0.05g, 0.217 mmol) was added and stirring was continued 16h at rt. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 ml) and shaken well. The aqueous layer was extracted with CH_2Cl (3 x 15 ml) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **179** (1.16g, 74% for 2 steps) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.22-

7.82 (m, 5H), 5.58 (s, 1H), 5.12 (s, 1H), 4.94 (s, 1H), 4.34 (s, 1H), 4.14, 4.06 (ABq, J_{AB} = 11.2 Hz, 2H), 1.76-1.82 (m, 1H), 1.72, (s, 3H), 1.05 (d, J = 7.0 Hz, 3H).



193

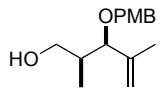
***p*-Methoxy benzylidene Acetal 193.** Anisaldehyde dimethyl acetal (4.8 ml, 28.3 mmol) was added to a stirred solution of crude diol **178** from above (25.8 mmol) in CH_2Cl_2 (90 ml). Camphor sulfonic acid (0.18g, 0.77 mmol) was added and stirring was continued 16h at rt. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (80 ml) and shaken well. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **193** (4.93g, 77% for 2 steps) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.89 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 9.0 Hz, 2H), 5.52 (s, 1H), 5.10 (s, 1H), 4.93 (s, 1H), 4.32 (s, 1H), 4.13, 4.04 (ABq, J_{aB} = 11.2 Hz, 2H), 1.74-1.80 (m, 1H), 1.70 (s, 1H), 1.05 (d, J = 8.0 Hz, 3H).



179 **180**

Alcohol 180. DIBAL-H (9.54 ml, 9.54 mmol) was added dropwise to a stirred, cooled (ice-H_2O bath) solution of benzylidene acetal **179** from above (0.83g, 3.92 mmol)

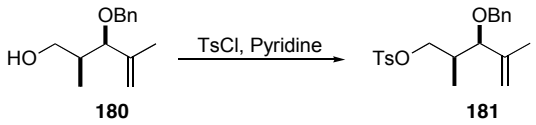
in CH_2Cl_2 (18 ml). Stirring was continued for 1h, the ice-H_2O bath was removed, and stirring was continued for 2h at rt. The reaction mixture was poured into a cooled (ice-H_2O bath) mixture of CH_2Cl_2 (30ml) and 0.5 M HCl (60 ml) and stirring was continued 30 min at rt. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 ml). The combined organics were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **180** (0.79g, 91%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.25-7.39 (m, 5 H), 5.06 (s, 1H), 5.01 (s, 1H), 4.71 (d, J = 8.0 Hz, 1H), 4.57, 4.23 (ABq, J_{AB} = 12.8 Hz, 2H), 3.72 (d, J = 8.0 Hz, 1H), 3.46-3.60 (m, 2H), 1.88-1.96 (m, 1H), 1.73 (s, 3H) 0.98 (d, J = 8.0 Hz, 3 H).



194

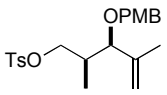
Alcohol 194. DIBAL-H (18.7 ml, 18.7 mmol) was added dropwise to a stirred, cooled (ice-H_2O bath) solution of benzylidene acetal **193** from above (1.86g, 7.50 mmol) in CH_2Cl_2 (35 ml). Stirring was continued for 1h, the ice-H_2O bath was removed, and stirring was continued for 2h at rt. The reaction mixture was poured into a cooled (ice-H_2O bath) mixture of CH_2Cl_2 (60ml) and 0.5 M HCl (120 ml) and stirring was continued 30 min at rt. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 ml). The combined organics were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel using 30:70 EtOAc-hexanes gave **194** (1.80g, 96%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.27 (d, J = 13.3 Hz, 2H), 6.89 (d, J = 13.3 Hz, 2H), 5.05 (s, 1H), 5.00 (s, 1H), 4.51, 4.18 (ABq, J_{AB} = 11.2 Hz, 2H), 3.80 (s, 3H),

3.70 (d, J = 8.0 Hz, 1H), 3.44-3.58 (m, 2H), 1.82-1.94 (m, 1H), 1.73 (s, 3H), 0.96 (d, J = 8.0 Hz, 3H).



180 **181**

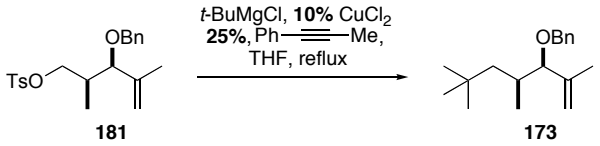
Tosylate 181. Tosyl chloride (0.57 g, 3.0 mmol) was added to a stirred solution of alcohol **180** (0.55 g, 2.50 mmol) in pyridine (12 mL). Stirring was continued 16h. The reaction was poured into a mixture of H_2O/ice and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 10% aqueous HCl (v/v) (5 mL) followed by brine (5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave **181** (0.79g, 85%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.20–7.31 (m, 9H), 4.96 (s, 1H), 4.89 (s, 1H), 4.45, 4.11 (ABq, J_{AB} = 12.0 Hz, 2H), 3.95 (dd, J = 5.3, 9.3 Hz, 1H), 3.76-3.82 (m, 1H), 3.61 (d, J = 6.7 Hz, 1H), 2.4 (s, 3H), 1.96-2.02 (m, 1H), 1.60 (s, 3H), 0.91 (d, J = 8.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 144.8, 141.9, 138.9, 133.0, 129.9, 128.4, 127.9, 127.7, 127.6, 114.6, 114.5, 82.7, 72.6, 70.6, 35.5, 21.7, 17.9, 12.1.



195

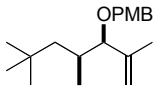
Tosylate 195. Tosyl chloride (1.65g, 8,65 mmol) was added to a stirred solution of alcohol **194** (1.80 g, 7.20 mmol) in pyridine (35 mL). Stirring was continued 16h. The reaction was poured into a mixture of H_2O/ice and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 10% aqueous HCl (v/v) (10 mL)

followed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **195** (2.42g, 83%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18 (d, *J* = 9.6 Hz, 2H), 6.82 (d, *J* = 9.6 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 4.98 (s, 1H), 4.91 (s, 1H), 4.41, 4.07 (ABq, J_{AB} = 13.3 Hz, 2H), 3.95 (dd, *J* = 5.3, 9.3 Hz, 1H), 3.78-3.82 (m, containing a s at 3.81, 4H), 3.60 (d, *J* = 6.6 Hz, 1H), 2.42 (s, 3H), 1.95-2.02 (m, 1H), 0.91 (d, *J* = 8.0 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 159.2, 155.9, 150.6, 144.8, 143.8, 143.5, 142.1, 137.1, 133.0, 130.6, 129.9, 129.4, 128.5, 128.0.



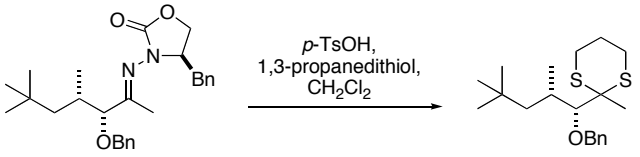
181 **173**

Olefin (173). *t*-BuMgCl (0.97 mL, 1.93 mmol, 2.0 M in THF) was added to a stirred solution of **181** (0.361 g, 0.963 mmol), copper(II) chloride (0.013 g, 0.096 mmol) and 1-phenyl-1-propyne (0.030 ml, 0.241 mmol) in THF (5 mL). The reaction mixture was heated to reflux for 24 h and then allowed to cool to rt. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture. Stirring was continued for 10 min. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc:hexane gave **173** (0.233g; 93%) as a pure, colorless oil. Spectroscopic data was identical to that reported above.



196

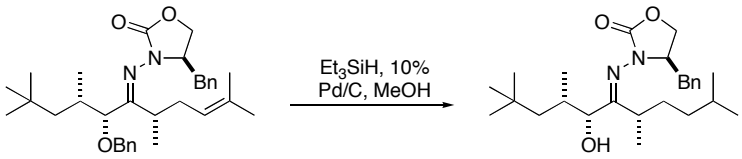
Olefin (196). *t*-BuMgCl (1.71 mL, 3.41 mmol, 2.0 M in THF) was added to a stirred solution of **195** (0.69 g, 1.71 mmol), copper(II) chloride (0.023 g, 0.17 mmol) and 1-phenyl-1-propyne (0.053 ml, 0.43 mmol) in THF (9 mL). The reaction mixture was heated to reflux for 24 h and then allowed to cool to rt. Saturated aqueous NH_4Cl (10 mL) was added to the reaction mixture. Stirring was continued for 10 min. The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc:hexane gave **196** (0.452 g; 91%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.25 (d, *J* = 10.6 Hz, 2H), 6.82 (d, *J* = 10.6 Hz, 2H), 5.03 (s, 1H), 4.89 (s, 1H), 4.45 (app. d, *J* = 11.0 Hz, 1H), 4.10-4.17 (m, 2H), 3.30 (d, *J* = 8.9 Hz, 1H), 1.62-1.79 (m, containing s at 1.67, 4H), 1.30-1.33 (m, 1H), 1.00 (d, *J* = 8.0 Hz, 3H), 0.85 (s, 9H).



175 **183**

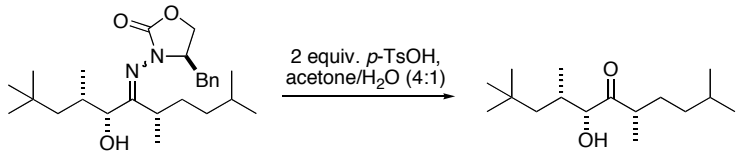
Dithiane 183. 1,3-propanedithiol (0.022 ml, 0.22 mmol) was added to a stirred, cooled (ice-H_2O bath) solution of hydrazone **175** (0.010g, 0.022 mmol) in CH_2Cl_2 (1 ml). *p*-TsOH (1.0mg, 0.004 mmol) was added and stirring was continued 16h at rt. The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$, dried over $MgSO_4$,

filtered, and evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc:Hexane gave **183** (4.0mg; 61%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30-7.41 (m, 5H), 4.62, 4.37 (ABq, J_{AB} = 12.0 Hz, 2H), 3.55 (d, J = 6.0 Hz, 1H), 2.80 (m, 1H), 2.65 (m, 1H), 1.88-2.20 (m, 3H), 1.66 (s, 3H), 1.32-1.38 (m, 2H), 1.01-1.07 (m, 2H), 0.98 (d, J = 8.0 Hz, 3H), 0.86 (s, 9H).



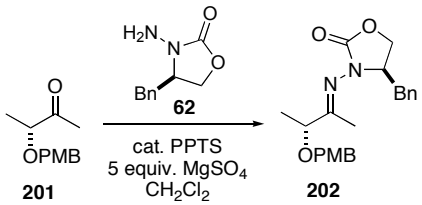
177 **188**

ACC hydrazone 188. 10% Pd/C (0.002g, 20% by wt) and triethylsilane (0.034 ml, 0.21 mmol) were added to a stirred solution of ACC hydrazone **177** (0.011g, 0.021 mmol) in methanol (1 ml). Stirring was continued 20h at rt, after which the reaction mixture was filtered through celite and evaporated under reduced pressure. Flash chromatography over silica gel, using 15:85 EtOAc:hexane gave **188** (8.5 mg; 94%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.18-7.35 (m, 5H), 4.30-4.38 (m, 3H), 4.04-4.12 (m, 1H), 3.44 (d, J = 8 Hz, 1H), 3.06-3.14 (m, 1H), 2.90-2.98 (m, 1H), 2.68-2.76 (m, 1H), 1.93-2.00 (m, 1H), 1.76-1.84 (m, 1H), 1.65 (dd, J = 4, 8 Hz, 1H), 1.52-1.58 (m, 1H), 1.22-1.28 (m, 3H) 1.13 (d, J = 8 Hz, 3H), 0.96 (s, 9H), 0.86-0.91 (m, 10H).



188 **191**

α-Hydroxy Ketone 191. *p*-TsOH (0.005 g, 0.026 mmol) was added to a stirred solution of α-Hydroxy Hydrazone **xx** (0.0054g, 0.013 mmol) in a 4:1 mixture of acetone:water (1.25 ml). Stirring was continued 40h at rt. The mixture was then quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was washed with brine (1 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc-Hexane gave **188** (3.10 mg; 93%) as a pure, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.29 (dd, *J* = 2.4, 5.0 Hz, 1H), 3.39 (d, *J* = 5.0 Hz, 1H), 2.64-2.74 (m, 1H), 1.98-2.03 (m, 2H), 1.65-1.69 (m, 1H), 1.48-1.54 (m, 2H), 1.11-1.19 (m, containing a d at 1.12, *J* = 6.8 Hz, 5H), 0.97 (s, 3H), 0.89 (m, 6H), 0.74 (d, *J* = 6Hz, 3H).



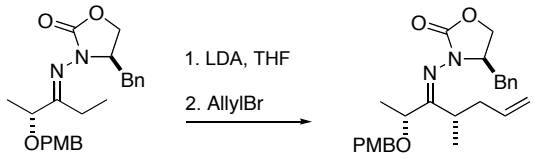
ACC Hydrazone 202. ACC auxiliary **62** (1.3 g, 3.74 mmol) was added to a stirred solution of Ketone **201** (0.59g, 2.88 mmol) and $MgSO_4$ (1.73g, 19.4 mmol) in DCM (15 ml). PPTS (0.03g, 0.014 mmol) was added and stirring was continued 24h at rt. The reaction was filtered, diluted with diethyl ether (20 ml), and washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave **202** (0.99g, 93%) as a pure, clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.85 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.22-7.38 (m, 5H), 4.54 (app. d, *J* = 12.0 Hz, 1H), 4.28-4.42 (m, 3H), 4.16 (q, *J* = 6.4 Hz, 1H), 4.81 (app. t, *J* = 8.0 Hz, 1H), 3.80 (s,

3H) 3.12 (dd, J = 4.0, 14.0 Hz, 1H), 2.77 (dd, J = 8.0, 14.0 Hz, 1H), 2.03 (s, 3H), 1.36 (d, J = 6.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 177.3, 159.3, 154.4, 135.6, 130.1, 129.8, 129.3, 128.9, 127.2, 113.9, 70.6, 66.8, 60.9, 55.4, 38.2, 19.3, 14.4.

202 **203**

Methylated ACC Hydrazone 203. *n*-BuLi (2.5 M in hexanes, 0.16 mL, 0.405 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.059 mL, 0.419 mmol) in THF (3 mL) (Ar atmosphere). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **202** (0.50 g, 0.135 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H_2O bath and stirred for 1h. After 1h the solution was cooled back down to –78 °C, methyl iodide (0.17 mL, 2.69 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **203** (0.049 g, 92%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.20-7.35 (m, 5H), 7.18 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.57 (app. d, J = 12.0 Hz, 1H), 4.33 (m, 2H), 4.28 (app. t, J = 9.3 Hz, 1H), 4.22 (q, J = 7.3, 1H), 4.07 (app. t, J = 9.3 Hz, 1H), 3.80 (s, 3H),

3.14 (dd, *J* = 4.0, 13.6 Hz, 1H), 2.73 (dd, *J* = 9.6, 13.6 Hz, 1H), 2.55-2.65 (m, 1H), 2.42-2.51 (m, 1H), 1.40 (d, *J* = 8.0 Hz, 3H), 1.16 (t, *J* = 8.8 Hz, 3 H).



203 **204**

Allylated ACC Hydrazone 204. *n*-BuLi (2.5 M in hexanes, 0.232 mL, 0.582 mmol) was added dropwise over ca. 2 min to a stirred and cooled (–78 °C) solution of diisopropylamine (0.084 mL, 0.601 mmol) in THF (1 mL) (Ar atmosphere). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **203** (0.077 g, 0.194 mmol) in THF (1 mL) was added by cannula, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H_2O bath and stirred for 1h. After 1h the solution was cooled back down to –78 °C, allyl bromide (0.067 mL, 0.776 mmol) was added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 1h and then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **204** (0.075 g, 89%) as a pure, light-yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.21-7.37 (m, 5H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.69-5.78 (m, 1H), 5.02-5. 09 (m, 2H), 4.56 (app. d, *J* = 11.2 Hz, 1H), 4.34-4.46 (m, 3H), 4.24 (app. t, *J* = 8.0 Hz, 1H), 4. 14 (app. t, *J* = 1.02 Hz, 1H), 3.80 (s, 3H), 3.16-3.24 (m, 2H), 2.65 (dd, *J* = 10.3, 13.7, 1H), 2.25-2.34 (m, 1H), 2.08-2.17 (m, 1H), 1.50 (d, *J* = 5.7 Hz, 3 H), 1.21 (d, *J* = 6.8, 3H).

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Biography

Emily Tarsis was born March 3, 1982 in Fort Thomas, Kentucky. She attended Coastal Carolina University from 2000-2004 after which she graduated *summa cum laude* receiving a B. S. in Chemistry with minors in Physics and Biology. She worked in the laboratory of Professor John Goodwin studying pentacooridinate (nitro) cobalt porphyrins. She also spent time at the University of Georgia (May-August 2004) working in the laboratory of Professor Michael Duncan studying metal-amino acid complexes. During her time at CCU, she was awarded the Coastal Scholars Award and the ACS Undergraduate Senior Chemistry Award.

In the Fall of 2005, she began her Ph. D. study in the Department of Chemistry at Duke University under the supervision of Professor Don M. Coltart where she changed her focuse to synthetic organic chemistry.

She receives her Ph. D. from Duke in December 2010 and will move to Jupiter, Florida, where she has accepted a postdoctoral position in the laboratory of Professor Glenn Micalizio at Scripps Research Institute.