Chapter 2

Efforts in Our Laboratory[‡]

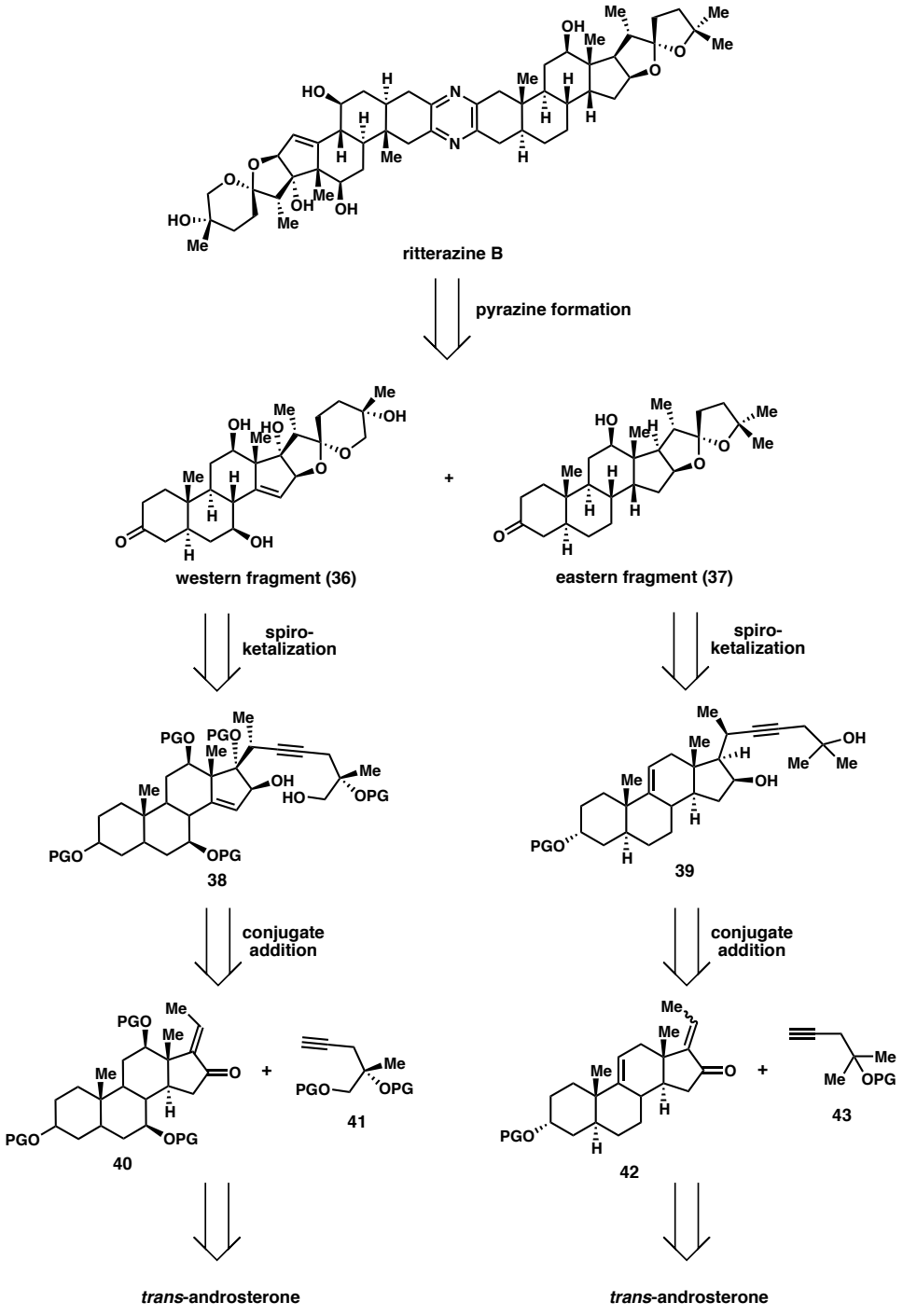
2.1 RETROSYNTHETIC ANALYSIS

Given that conditions for pyrazine formation have been established in prior synthetic reports by Shair and Fuchs,[2,6,8,9] ritterazine B was retrosynthetically simplified to the western (**36**) and eastern (**37**) fragments (**Scheme 9**). From here, our proposed retrosynthesis involves two key reactions, which can be employed for both halves of the natural product. We envision forming the 5/6 spiroketal of the western half and the 5/5 spiroketal of the eastern fragment using a metal-catalyzed alkyne spiroketalization reaction with intermediates **38** and **39**, respectively. These compounds can be produced from an alkyne conjugate addition between **40** and **41** for the western fragment, and between **42** and **43** for the eastern half. It is anticipated that for the western fragment, cyclization of the less hindered primary alcohol will occur to produce the 5/6 spirocycle. Enones **40** and **42** can be formed from commercially available steroid *trans*-androsterone (**24**). Specific issues that need to be addressed include improving upon existing methods to oxidize the C12 position, which is relevant for both halves of ritterazine B. In addition, for the western

[‡] Work conducted in collaboration with Anton Dubrovskiy and Arthur Han.

fragment, new strategies to oxidize carbons C7 and C17 and install the C14–C15 olefin are required.

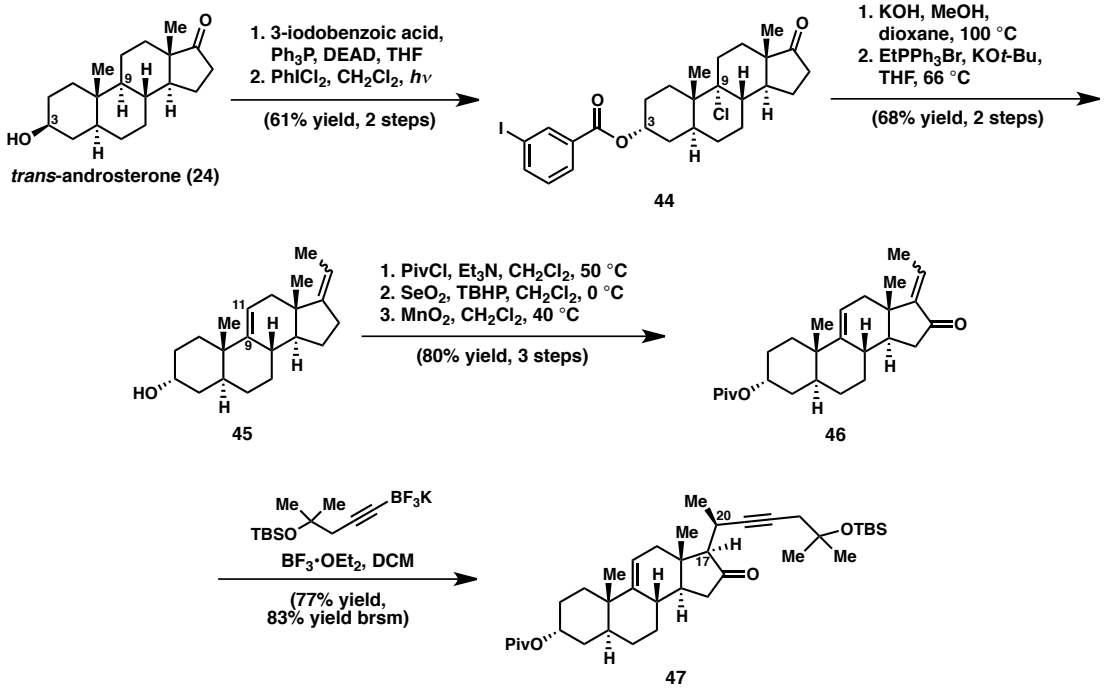
Scheme 9. *Retrosynthetic analysis of ritterazine B.*



2.2 SYNTHESIS OF THE EASTERN FRAGMENT

Initial studies in our laboratory were conducted by Anton Dubrovskiy and focused on the synthesis of the eastern fragment of ritterazine B beginning from commercially available *trans*-androsterone (**24**). The sequence begins with a Mitsunobu reaction between *trans*-androsterone (**24**) and 3-iodobenzoic acid to provide ester **44** with inversion of stereochemistry at C3 (**Scheme 10**). Directed C–H chlorination following the protocol developed by Davitishvili et al. furnished chloride **44** in 61% yield over two steps.[11] Subsequent elimination of the chloride to yield the C9–C11 olefin occurs with concomitant deprotection of the C3 alcohol, which upon Wittig olefination with $EtPPh_3Br$ produces olefin **45** in 68% yield over two steps. Protection of the alcohol as the pivalate ester followed by allylic oxidation with SeO_2 provided the C16–alcohol, which was oxidized with MnO_2 to provide enone **46**. After considerable experimentation, it was determined that addition of the alkynyl trifluoroborate salt to enone **46** in the presence of BF_3•OEt_2 furnished alkyne **47** in 77% yield.[12,13]

Scheme 10. *Initial steps of our synthesis of ritterazine B eastern fragment.*

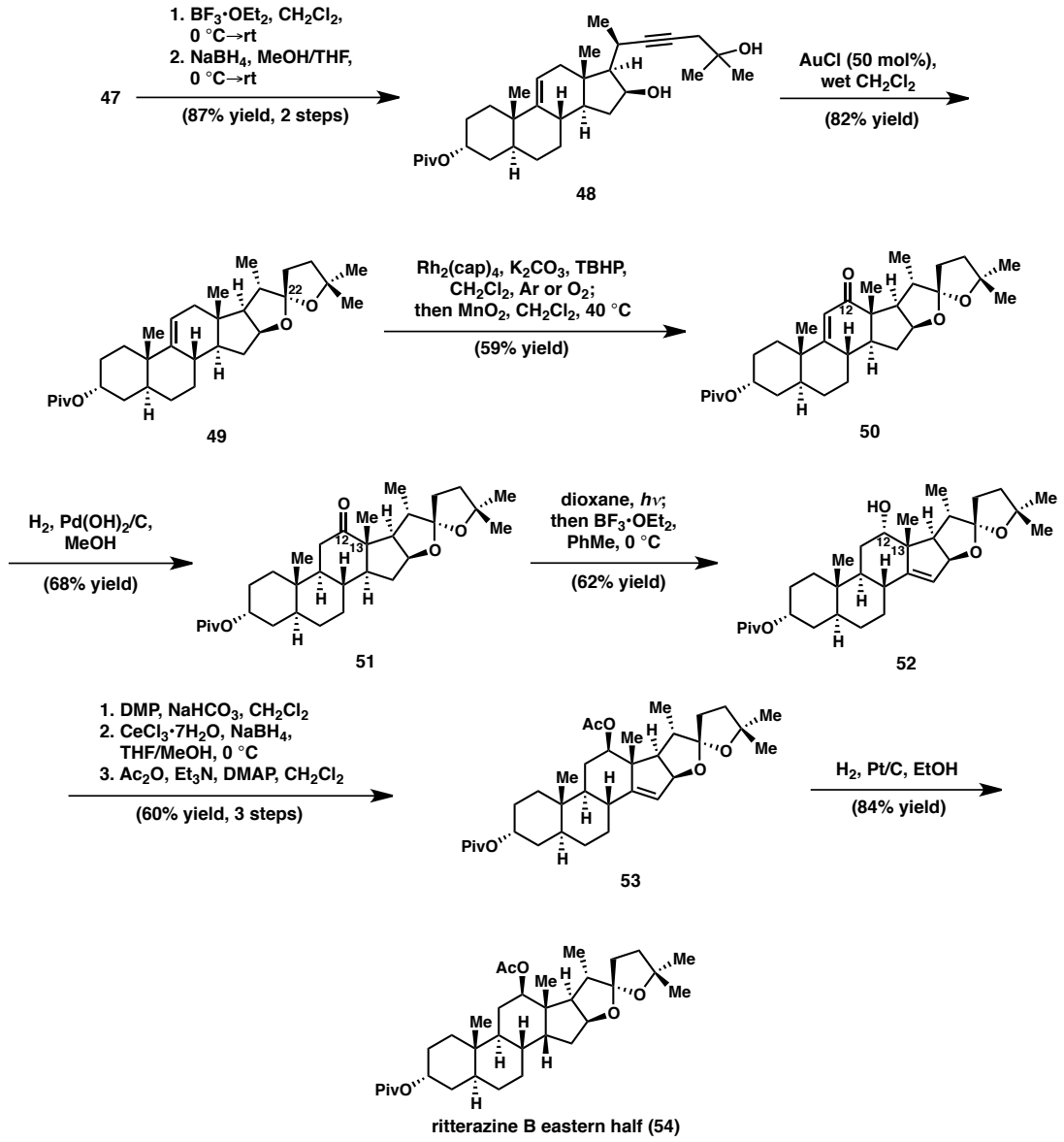


To prepare the spiroketalization precursor, silyl ether **47** was deprotected and the ketone was reduced to the desired β-configured alcohol to give diol **48** (**Scheme 11**). We were pleased to find that spiroketalization of **48** proceeded smoothly with catalytic AuCl to provide **49** with the correct stereochemistry at C20 and C22.[14] Notably, under the reaction conditions, C20 epimerizes to give the correct configuration. An allylic oxidation of **49** using catalytic $Rh_2(cap)_4$, K_2CO_3, and TBHP under argon or O_2 furnished enone **50**.[15] Hydrogenation of the C9–C11 olefin with $Pd(OH)_2/C$ produced **51** in 68% yield.

The final transformation required to complete the synthesis of ritterazine B eastern fragment is conversion of the C/D ring juncture from *trans* to *cis*. Adapting conditions from Shair, Norrish type I fragmentation of the C12–C13 bond and

subsequent closure via a BF_3•OEt_2-mediated ene reaction provided intermediate **52**.[2] Correction of the configuration of the C12 hydroxyl was achieved through oxidation/reduction. Following acetylation of the free hydroxyl group, hydrogenation produced the desired *trans* junction, completing the synthesis of the eastern fragment (**54**) in 15 steps from *trans*-androsterone.

Scheme 11. *Completion of our synthesis of the eastern fragment of ritterazine B.*

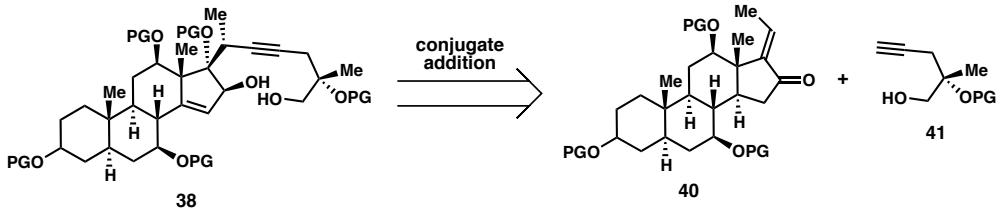


2.3 SYNTHESIS OF THE WESTERN FRAGMENT

2.3.1 Plan 1 – Alkyne Conjugate Addition

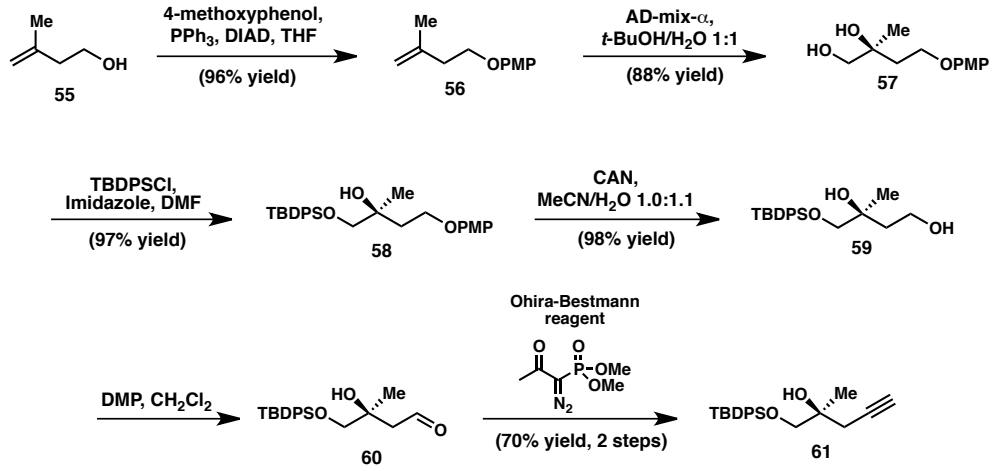
Given our success in preparing the eastern fragment of ritterazine B, my objective was to develop a synthesis of western fragment **38**. The initial goal was to investigate the conjugate addition reaction of alkyne **41**, as this is the first key step in our retrosynthesis (repeated in **Scheme 12**). Although alkyne **41** bears an additional hydroxyl group compared to the alkyne **43** (see **Scheme 9**), we anticipated using a similar sequence to that employed for the preparation of **47** (see **Scheme 10**).

Scheme 12. *Retrosynthetic analysis of first key reaction of the western fragment.*



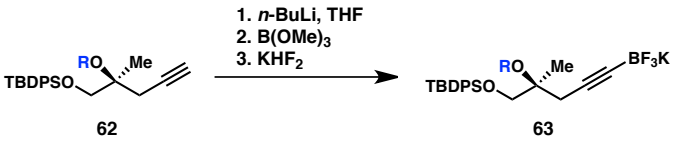
To this end, the desired alkyne **61** was initially prepared by a route adapted from a procedure published by Shair.[2] Starting with 3-methyl-3-buten-1-ol (**55**), protection of the alcohol group as the para-methoxy phenol (PMP) ether gave **56** in 96% yield (**Scheme 13**). Asymmetric dihydroxylation provided diol **57**, and selective protection of the primary alcohol as the *tert*-butyldiphenyl silyl (TBDPS) ether provided **58** in 97% yield. Deprotection of the PMP group, and then DMP oxidation produced aldehyde **60**. Finally, the Ohira-Bestmann reagent was employed to convert the aldehyde to the desired alkyne **61** in 70% yield over two steps.

Scheme 13. *Initial synthesis of alkyne fragment.*



The benefit of intermediate **61** is that several protecting group schemes could be investigated to find the optimal substrate for the conjugate addition reaction. Whereas treatment of **62a** (R = MOM) or **62b** (R = TES) with *n*-BuLi, $B(OMe)_3$, then KHF_2 provided the corresponding trifluoroborates (**Table 2**, entries 1 and 2), we were surprised to find that no reaction occurred under the same conditions with **62c** (R = TBS). The origin of this difference in reactivity is unclear, however it is possible that the increased steric hindrance of TBS is responsible for the lack of reactivity.

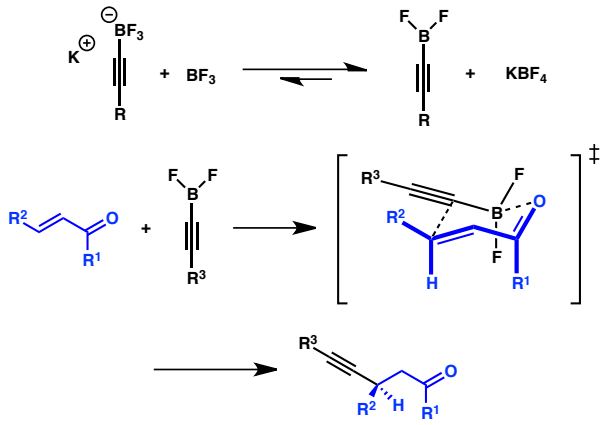
Table 2. *Initial attempts to form alkynyl trifluoroborate salt.*



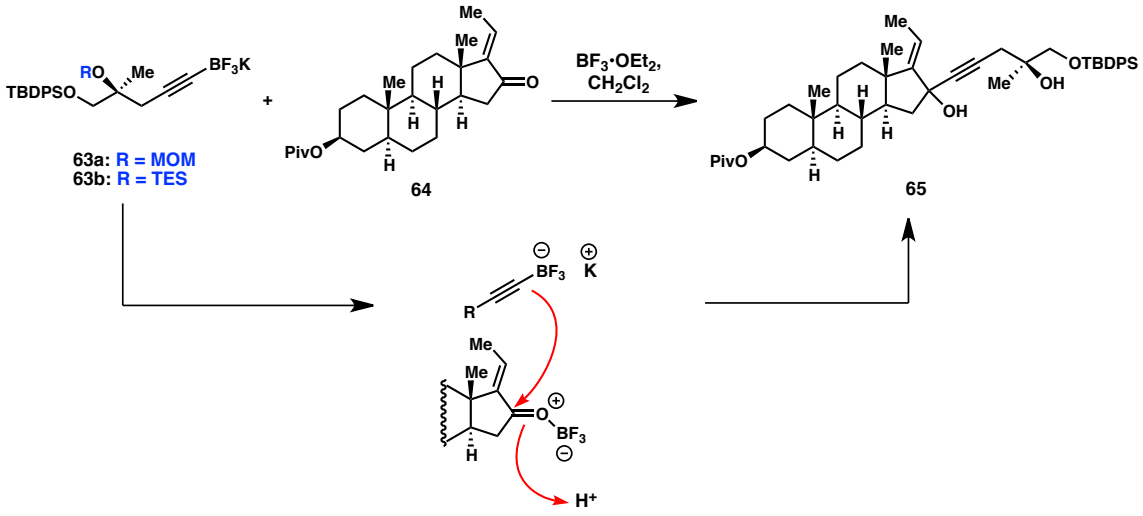
Entry	R	Result	63
1	MOM	82% yield	63a
2	TES	80% yield	63b
3	TBS	SM	63c

With trifluoroborates **63a** and **63b** in hand, the key conjugate addition reaction was investigated. Woodward et al. have shown that conjugate additions of alkynyl trifluoroborates to enones proceed through a closed transition state (**Scheme 14**).[13] In the presence of BF_3, the trifluoroborate salt is in equilibrium with the more active alkynyl BF_2 species, which forms a chair–like closed transition state that facilitates alkyne addition in a 1,4 fashion.[13] Unfortunately, under the previously optimized conditions, treatment of enone **64** with either trifluoroborate salts **63a** or **63b** gave only 1,2–addition product **65a** and **65b** (**Scheme 15**). Interestingly, the tertiary alcohol in the product was deprotected under the reaction conditions in both cases. A possible mechanism to produce **65** involves activation of the ketone with BF_3, followed by nucleophilic attack of the trifluoroborate salt at the carbonyl carbon.

Scheme 14. *Mechanism and transition state of alkyne conjugate addition using trifluoroborate salts.*

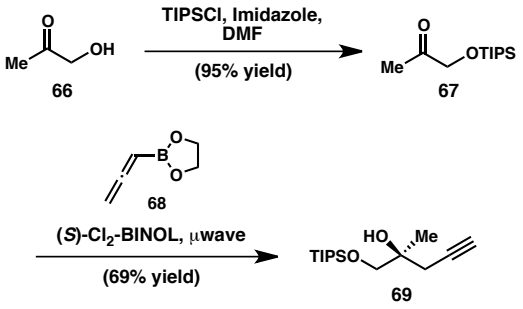


Scheme 15. *First attempt at conjugate addition.*



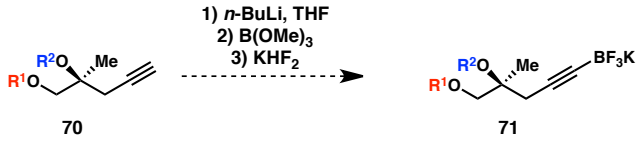
To determine whether the primary alcohol protecting group exerts any influence on the reactivity of the conjugate addition, further alkynyl derivatives were prepared. However, the synthesis of the alkyne fragment (shown in **Scheme 13**) did not lend itself to late stage diversification. Therefore, a more rapid and efficient synthesis of the alkyne fragment was developed based on a catalytic asymmetric reaction reported by Shaus et al. (**Scheme 16**).[16] Beginning with hydroxyacetone (**66**), the free alcohol was protected as the tri-*iso*-propylsilyl (TIPS) ether (**67**). Treatment of **67** with allenylboronate **68** and catalytic BINOL under microwave irradiation produced **69** in 62% yield. This route has proven to be significantly more convenient and has greatly improved the synthesis of the alkyne fragment.

Scheme 16. *Improved synthesis of alkyne fragment.*



After protection of the tertiary alcohol of **69** as the TBS ether, this compound was subjected to the standard conditions for trifluoroborate formation. Unfortunately, no reaction occurred and starting material was recovered (entry 1, **Table 3**). Attempts to change the identity of the tertiary alcohol protecting group of **69** were unsuccessful. Therefore, we turned our attention to altering the primary alcohol protecting group. Disappointingly, efforts to convert the bis-silyl ethers **70b** and **70c** to their corresponding trifluoroborates were also unsuccessful (entries 2 and 3).

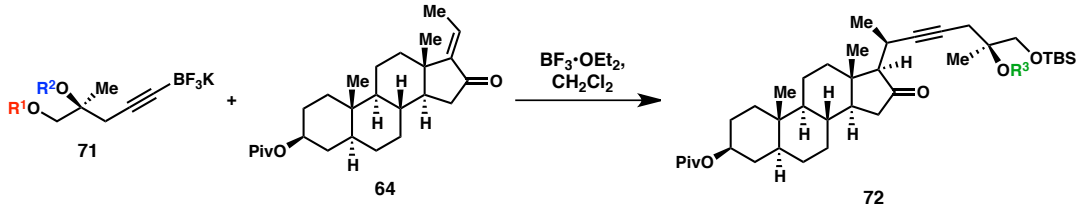
Table 3. *Attempts to form the desired trifluoroborate salt.*



Entry	R^1	R^2	Result	71
1	TIPS	TBS	SM	71a
2	TBS	TIPS	SM	71b
3	TBS	TBS	SM	71c

Concomittant to my own efforts, my co-workers were also preparing alkynyl trifluoroborates with varying protecting groups. This collective effort determined that alkynyl trifluoroborates **71a** and **71b** can be prepared, and that these compounds will undergo the desired conjugate addition reactions in 25% and 56% yield respectively.

Table 4. *Most current results with the conjugate addition reaction.*



Entry	R^1	R^2	Result	72	R^3
1	All	TBS	~25% NMR yield	72a	H
2	PMP	Me	56% isolated yield	72b	Me

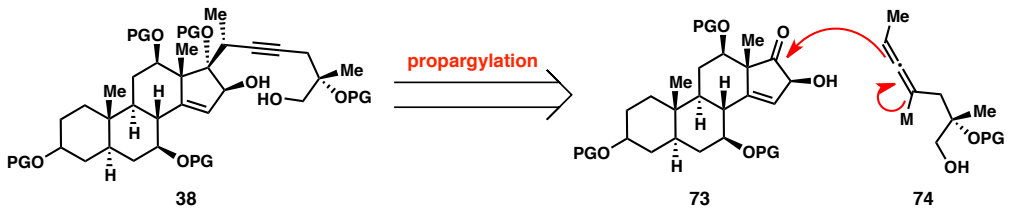
Future directions of this synthetic route involve applying the alkynyl conjugate addition to a fully oxidized western steroid. Most importantly, methods to oxidize at C17 following the conjugate addition reaction must be investigated. One possible approach would involve a Rubottom oxidation of a silyl enol ether derived from **72**. Although this route seems probable, alternative routes with potentially shorter step counts were also pursued.

2.3.2 Plan 2 – Propargylation with Allenes

An alternative route to intermediate **38** has been explored. This approach involves the propargylation of α-hydroxyketone **73** with functionalized allenyl metal

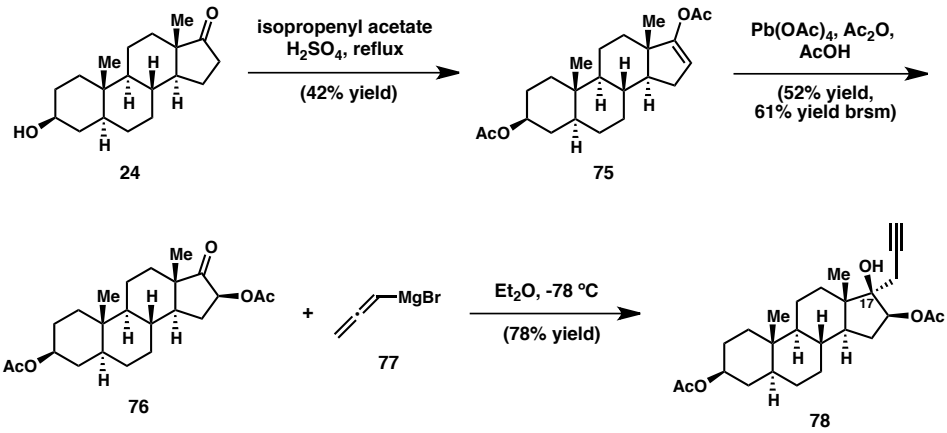
74 (**Scheme 17**). This type of reaction has been developed using a variety of allenyl metal species, including tin,[17] magnesium,[18] lithium,[19] titanium,[20] boron,[21] and zinc,[22] as well as others. Most allenyl metal reagents are unstable, and are therefore generated in situ.[17a] A complicating factor is that these reagents are often in equilibrium with the propargylic species, however sufficient research has been done to favor the propargylic adduct.[17a] Although the diastereoselectivity of the transformation was initially uncertain, this route is attractive in that the C17 alcohol would be installed directly during the propargylation reaction.

Scheme 17. *Revised retrosynthesis of intermediate* ***38*** *using propargylation.*



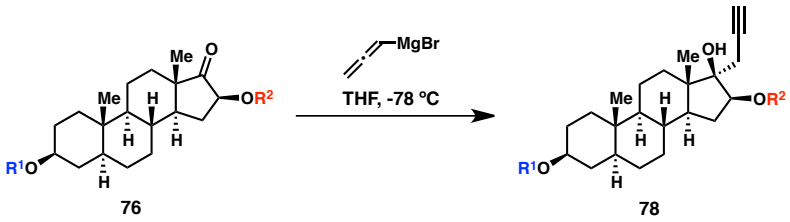
In order to investigate this reaction, model steroid *trans*-androsterone (**24**) was oxidized α to the carbonyl using the two-step procedure reported by Ridley et al. (**Scheme 18**).[23] Treatment of **24** with isopropenyl acetate and catalytic sulfuric acid at reflux produced protected enolate **75**, which upon subsequent oxidation with lead(IV) acetate provided α-acetoxy ketone **76** in 52% yield (61% yield b.r.s.m.). We were pleased to find that exposure of **76** at –78 °C to allenylmagnesium bromide (**77**), generated in situ from propargyl bromide, produced homopropargyl alcohol **78** in 78% yield. Moreover, alcohol **78** was produced as a single diastereomer.

Scheme 18. *Initial hit in propargylation studies with model ketone.*



Unfortunately, stereochemical analysis by 1D- and 2D-NMR determined that **78** possesses the incorrect configuration at C17. In an effort to overturn this diastereoselectivity, a variety of protecting groups capable of directing delivery of the allenyl Grignard were initially pursued. **Table 5** shows the results of substrates bearing different protecting groups with allenyl Grignard. Unfortunately, treatment of the substrates under standard conditions still resulted in allenylation to give the undesired propargylation product.

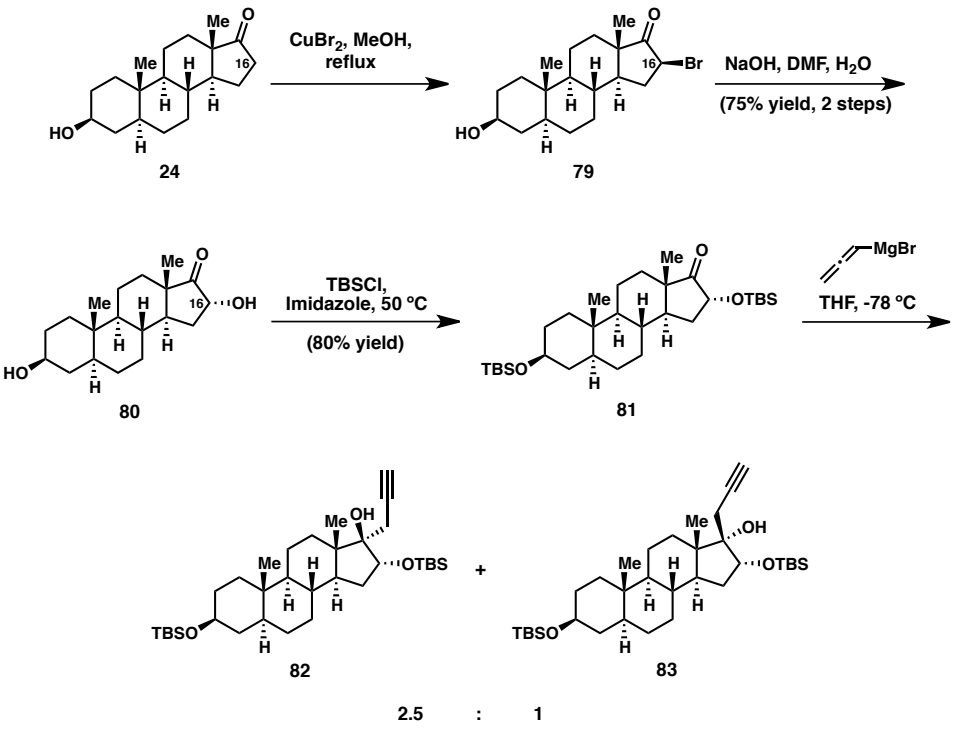
***Table 5**. Reaction of allenyl Grignard with directing protecting groups.*



Entry	R^1	R^2	Result
1	H	H	side product
2	MOM	MOM	78b (72% yield)
3	MEM	MEM	78c (63% yield)

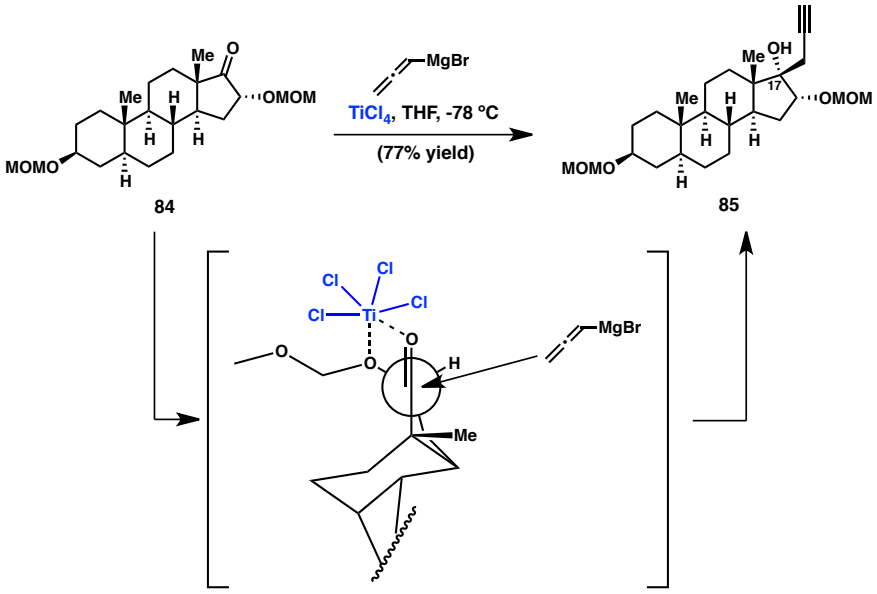
Given the lack of success overturning the diastereoselectivity on the β-disposed C16 hydroxyl, we turned our attention to investigating the propargylation of steroids bearing the inverted stereochemistry at position C16. We hypothesized that a large sterically bulky protecting group would block the α-face, directing propargylation to the β-face. Diol **80** was prepared using a two-step procedure developed by Numazawa and Osawa et al. by performing an α-bromination, followed by S_N2 displacement (**Scheme 19**).[24] After TBS protection to form **81**, propargylation with allenyl Grignard resulted in a mixture of diastereomers **82**/**83** 2.5:1 d.r. Although the major diastereomer **82** is the undesired stereochemistry, formation of the desired product **83** was a promising result.

Scheme 19. *Propargylation with α-configuration at C16.*



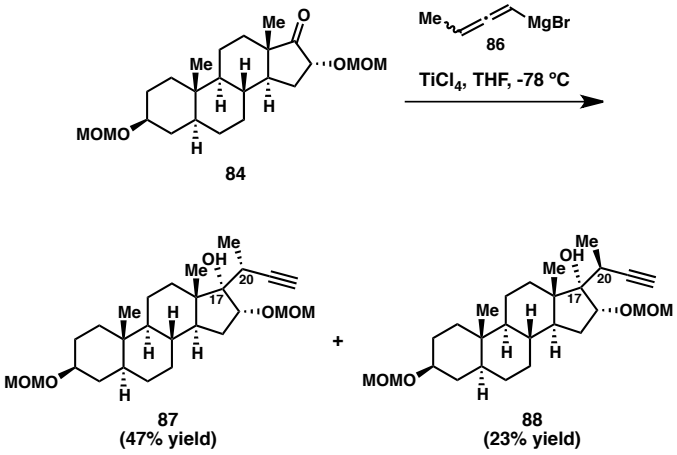
Reetz et al. have demonstrated that diastereoselectivity of propargylation reactions can be influenced by using $TiCl_4$ as an additive.[25] It is proposed that $TiCl_4$ can coordinate to the carbonyl oxygen, as well as oxygen atoms of an ether protecting group, and promote propargylation through an open transition state. Inspired by Reetz's findings, compound **84** was prepared and subjected to allenyl Grignard and $TiCl_4$ in dichloromethane at –78 °C (**Scheme 20**). Much to our pleasure, homopropargyl alcohol **85** was formed in 77% yield as a single diastereomer, with the correct stereochemistry at C17.

Scheme 20. *Propargylation with $TiCl_4$ to form the desired stereochemistry at C17.*



Having achieved the desired stereoselectivity, we turned to investigating more complex allenyl Grignard reagents. Reaction of steroid **84** with methylated allenyl Grignard **86**, prepared from 3-bromo-1-butyne, produced a mixture of two diastereomers **87** and **88** in 47% and 23% yields, respectively (**Scheme 21**). These two diastereomers arise from the fact that Grignard **86** is racemic; it was anticipated that the enantioenriched allene would deliver the desired product with high diastereoselectivity.

Scheme 21. *Initial attempts at propargylation with methylated allenyl Grignard* ***86***.



To investigate the diastereoselectivity with a chiral allene, a protocol was adapted from Marshall et al.[26] Beginning with (S)-(–)-butyn-2-ol (**89**), attempts to isolate chiral bromide **90** were unsuccessful due to volatility of the bromide (**Scheme 22**). As an alternative intermediate, mesylate **91** was formed as a precursor for the chiral allenyl zinc reagent **92**. Upon treatment of steroidal ketone **84** with zinc reagent **92**, homopropargyl alcohol **87** was formed as a single diastereomer, and the structure of **87** was confirmed via X-ray crystallography (**Figure 4**) to verify the stereochemistry at C20.

Scheme 22. *Propargylation with chiral allenyl zinc reagent.*

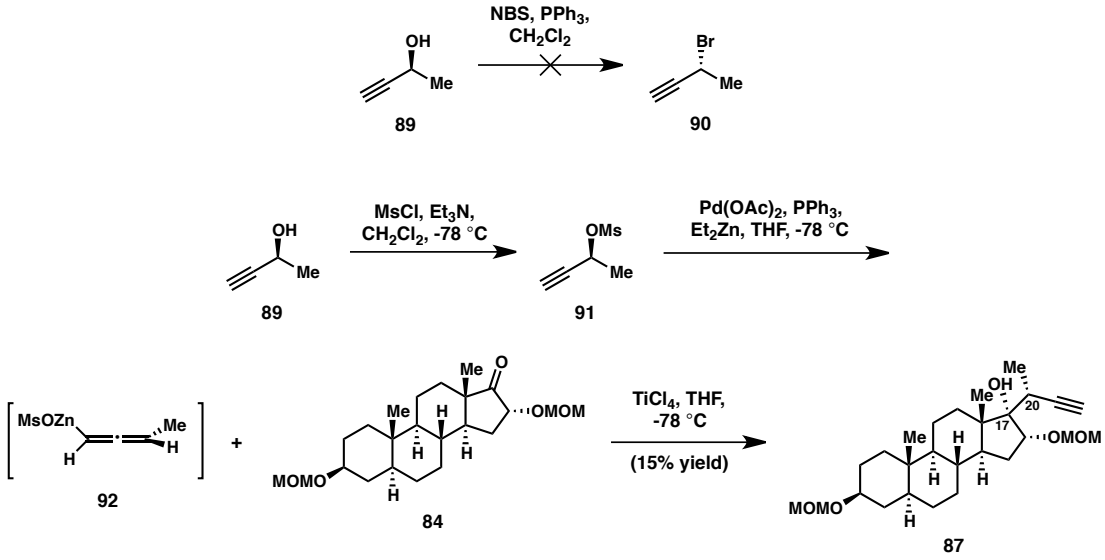
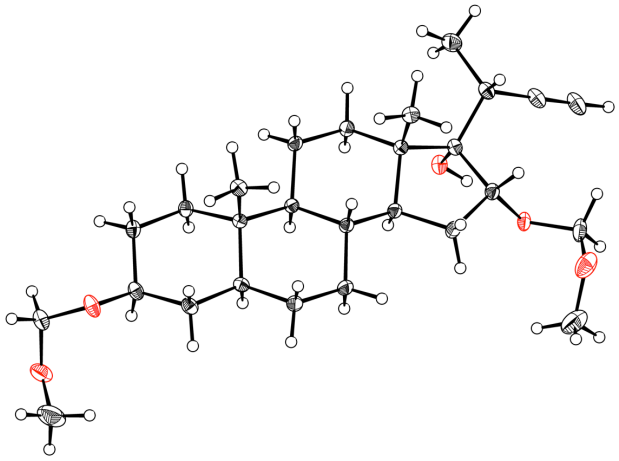


Figure 4. *X-ray structure of alcohol **87**.*

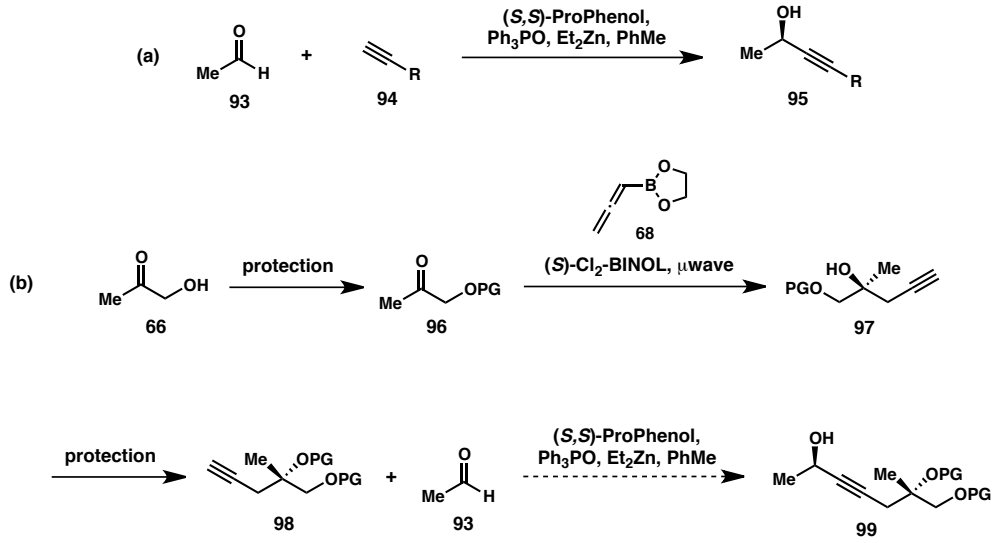


2.4 FUTURE DIRECTIONS

The next step in investigating the synthetic utility of the propargylation reaction in the total synthesis of ritterazine B would be to incorporate the oxygenated aliphatic chain on the alkyne. An efficient method to accomplish this goal involves a

reaction developed by Trost et al. that forms chiral propargyl alcohols **95** from acetaldehyde (**93**) and terminal alkynes **94** (**Scheme 23a**).[27] Using our previously established conditions to form the protected alkyne fragment **98**, the desired chiral homopropargyl alcohol **99** can be synthesized in four steps (**Scheme 23b**).

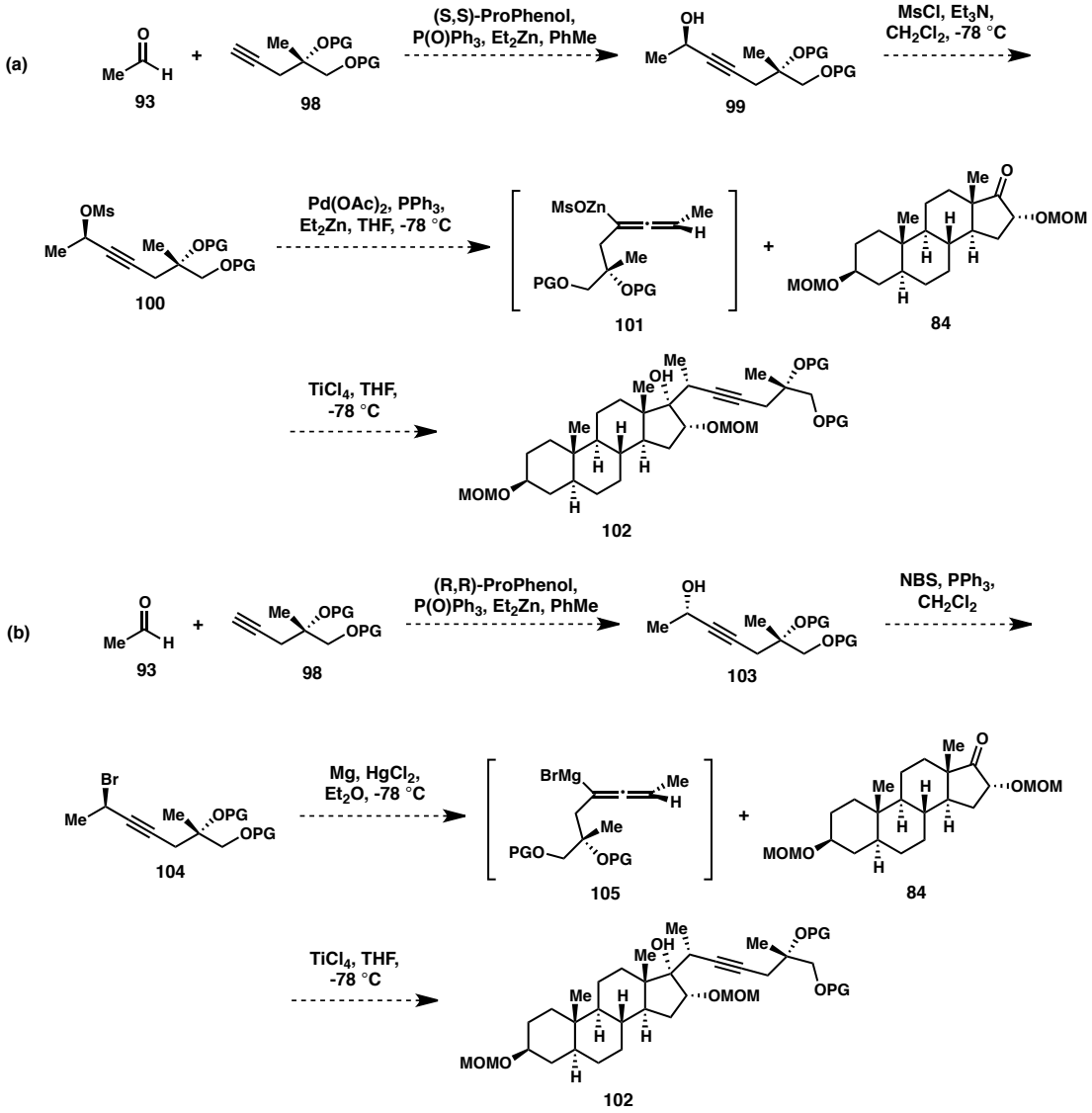
Scheme 23. *(a) Formation of chiral propargyl alcohols by Trost et al. (b) Plan to form desired propargyl alcohol using Trost's method.*



With alcohol **99** in hand, there are two possible conditions for the propargylation reaction with steroid **84** that could deliver the desired product. The first set of conditions utilizes chiral allenyl zinc mesylate **101**, which is formed from the corresponding mesylate **100** (**Scheme 24a**). Treatment of **84** with zinc mesylate **101** will produce homopropargyl alcohol **102**. However, since the yield of the propargylation reaction with allenyl zinc **92** (see **Scheme 22**) was low yielding, either optimization of these conditions or investigation of a different metal are required. Using the (*R*,*R*)-ProPhenol ligand in the Trost reaction with acetaldehyde (**93**) and

alkyne **98** delivers *R*-alcohol **103**, which will undergo an S_N2 reaction to form bromide **104** as a precursor to the chiral allenyl Grignard **105** (**Scheme 24b**). Treatment of steroid **84** with in situ-generated Grignard **105** should produce the desired homopropargyl alcohol **102**.

Scheme 24. *Plans to produce homopropargyl alcohol **102** (a) using a chiral allenyl zinc mesylate or (b) using a chiral allenyl Grignard.*



In order to utilize the propargylation reaction in the synthesis of the western fragment of ritterazine B, the steroid substrate needs to be oxidized at C7 and C12 prior to the propargylation reaction. *trans*-Dehydroandrosterone **103** will be oxidized at C12 using Shair's two-step procedure to provide **104**,[2] followed by ketone protection, oxidation at C7, hydrogenation, and ketone deprotection to deliver compound **105** (**Scheme 25**). To access propargylation substrate **106**, intermediate **105** undergoes α-bromination and S_N2 displacement, and treatment of **106** with a chiral allene **107** will produce homopropargyl alcohol **108**. To install the double bond at C14–C15, the tertiary alcohol is protected, C16 MOM ether is deprotected, oxidized, and a Mukaiyama reaction will provide enone **109**. Reduction at C16 to alcohol **110**, followed by primary alcohol deprotection and alkyne spiroketalization should produce ritterazine B western fragment **111**. This substrate can be coupled with the eastern half of ritterazine B via pyrazine formation to complete the total synthesis of ritterazine B.

Scheme 25. *Plans to complete the synthesis of ritterazine B western fragment.*