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 EtPPh3Br produces olefin 45 in 68% yield over two steps. Protection of the alcohol as the pivalate ester followed by allylic oxidation with SeO2 provided the C16–alcohol, which was oxidized with MnO2 to provide enone 46. After considerable experimentation, it was determined that addition of the alkynyl trifluoroborate salt to enone 46 in the presence of BF3•Et2 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. Notably, under the reaction conditions, C20 epimerizes to give the correct configuration. An allylic oxidation of 49 using catalytic Rh2(cap)4, K2CO3, and TBHP under argon or O2 furnished enone 50. 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${}_3\cdot$OEt$_2$-mediated ene reaction provided intermediate 52. 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-butylidiphenyl 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.

![Scheme 13](image)

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 KHF₂ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Result</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MOM</td>
<td>82% yield</td>
<td>63a</td>
</tr>
<tr>
<td>2</td>
<td>TES</td>
<td>80% yield</td>
<td>63b</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>SM</td>
<td>63c</td>
</tr>
</tbody>
</table>
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). In the presence of BF₃, the trifluoroborate salt is in equilibrium with the more active alkynyl BF₂ species, which forms a chair–like closed transition state that facilitates alkyne addition in a 1,4 fashion. 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 BF₃, 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.
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).\(^6\) 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Result</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS</td>
<td>TBS</td>
<td>SM</td>
<td>71a</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>TIPS</td>
<td>SM</td>
<td>71b</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>TBS</td>
<td>SM</td>
<td>71c</td>
</tr>
</tbody>
</table>
Concomitant 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.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Result</th>
<th>$72$</th>
<th>$R^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All</td>
<td>TBS</td>
<td>~25% NMR yield</td>
<td>72a</td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>PMP</td>
<td>Me</td>
<td>56% isolated yield</td>
<td>72b</td>
<td>Me</td>
</tr>
</tbody>
</table>

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 $\alpha$-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,\textsuperscript{17} magnesium,\textsuperscript{18} lithium,\textsuperscript{19} titanium,\textsuperscript{20} boron,\textsuperscript{21} and zinc,\textsuperscript{22} as well as others. Most allenyl metal reagents are unstable, and are therefore generated in situ.\textsuperscript{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.\textsuperscript{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 \( \alpha \) to the carbonyl using the two-step procedure reported by Ridley et al. (Scheme 18).\textsuperscript{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 \( \alpha \)-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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>side product</td>
</tr>
<tr>
<td>2</td>
<td>MOM</td>
<td>MOM</td>
<td>78b (72% yield)</td>
</tr>
<tr>
<td>3</td>
<td>MEM</td>
<td>MEM</td>
<td>78c (63% yield)</td>
</tr>
</tbody>
</table>

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<sub>N</sub>2 displacement (Scheme 19). 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.\textsuperscript{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.
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.\textsuperscript{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). 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\textsubscript{N}2 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, 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 S₅N₂ 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.