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Communication

Total Synthesis of Ritterazine B

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ABSTRACT: The first total synthesis of the cytotoxic alkaloid ritterazine B is reported. The synthesis features a unified approach to both steroid subunits, employing a titanium-mediated propargylation reaction to achieve divergence from a common precursor. Other key steps include gold-catalyzed cycloisomerizations that install both spiroketals and late stage C−H oxidation to incorporate the C7′ alcohol.

Ritterazine B (**1**) is a bis-steroidal pyrazine (BSP) natural product that was isolated in 1995 from the marine tunicate *Riterella tokioka* off of Japan's Izu Peninsula.[1] The BSPs include some of the most potent anticancer compounds discovered to date,[2] and **1**, in particular, has been described as "among the most potent growth inhibitors ever tested" by the National Cancer Institute (NCI).[3−5] It possesses subnanomolar activity against P388 leukemia cells (0.17 nM IC_{50})[6] and an average GI_{50} of 3.2 nM in the NCI-60 cell line screen.[5,7] Given that the BSPs display distinct activity patterns in NCI-60 COMPARE analyses, they are proposed to act by a distinct mode of action from existing chemotherapies.[4,7,8]

Although the BSPs are known to induce apoptosis,[3] a lack of natural material has hampered translational investigations of **1** and related compounds. Landmark studies from Shair and coworkers implicated BSPs as high-affinity ligands for oxysterol binding proteins,[4] while more recent evidence indicates that the endoplasmic reticulum-specific heat-shock protein GRP78 may be their efficacious target.[9,10] Given these promising foundational studies, improved synthetic access to **1** is required to fully evaluate its potential as a chemotherapeutic.[2,8] In this communication, we report the first total synthesis of **1**. Our approach uses a common strategy to prepare both of the steroid spiroketals from *trans*-dehydroandrosterone, a commercially available and inexpensive steroid.

In line with prior efforts to the BSPs,[5,11] our retrosynthetic analysis began with scission of the central pyrazine ring, revealing the "western" and "eastern" steroids **2** and **3**, respectively (Figure 1). To streamline our route development, we sought to prepare both **2** and **3** from a common starting material, using the same general tactics for C−C bond formation and spiroketalization. In this vein, steroids **2** and **3** were simplified to the corresponding alkynes **4** and **5**, where transition metal-catalyzed cycloisomerization[12] would be used to form the respective spiroketals. This retrosynthetic step shifted the synthetic challenge to the union of differentiated alkyne fragments with a common steroid core. We envisioned preparing alkynes **4** and **5** by 1,2-addition of the propargyl-metal species derived from **6** or **7** to an α-hydroxy ketone accessible from *trans*-dehydroandrosterone (**8**). The choice of **8** as the starting material was seen as strategic: the C5−C6 alkene would provide a handle for late-stage B-ring oxidation. This tactic has yet to be utilized in synthetic approaches to the BSPs,[11] which could be why BSPs with C7/C7′ oxidation have not previously been synthesized.[7]

In the forward sense, known steroid **9** (prepared in two steps from **8**)[13] was treated with excess *tert*-butyldimethylsilyl triflate and triethylamine (Et_3N) to protect the C3 and C12 alcohols and form the silyl enol ether at C17 (Scheme 1A). Direct addition of isopropanol and *N*-bromosuccinimide to the reaction mixture afforded α-bromoketone **10** in quantitative yield in one pot. Elimination of the C16 bromide under basic conditions gave an inconsequential mixture of isomeric enones ($\Delta^{14,15}$ and $\Delta^{15,16}$ not shown), which converged to dienol ether **11** on treatment with Et_3N and trimethylsilyl triflate. Selective epoxidation of the C16−C17 alkene with dimethyldioxirane and subsequent addition of tetrabutylammonium fluoride (TBAF) provided α-hydroxyketone **12** in 92% yield, which would serve as our divergent intermediate.

At this stage, we turned our attention to preparing the distinct spiroketals found in the western and eastern steroids **2** and **3**, respectively. To this end, titanium-mediated propargylations based on conditions reported by Sato and coworkers proved uniquely effective (Scheme 1B).[14] Deprotonation of the C16 alcohol by treatment of **12** with *n*-butyllithium, followed by addition of the organotitanium species derived from either propargyl bromide **6** or **7** resulted in 1,2-addition to give alkyne **13** in 54% yield or **14** in 56% yield. These additions occurred with exclusive β-face selectivity despite the axial methyl group,[15] possibly due to the formation of an α-disposed cyclic chelate between the C16 and C17 oxygens. While excellent diastereoselectivity was obtained at

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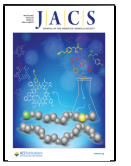

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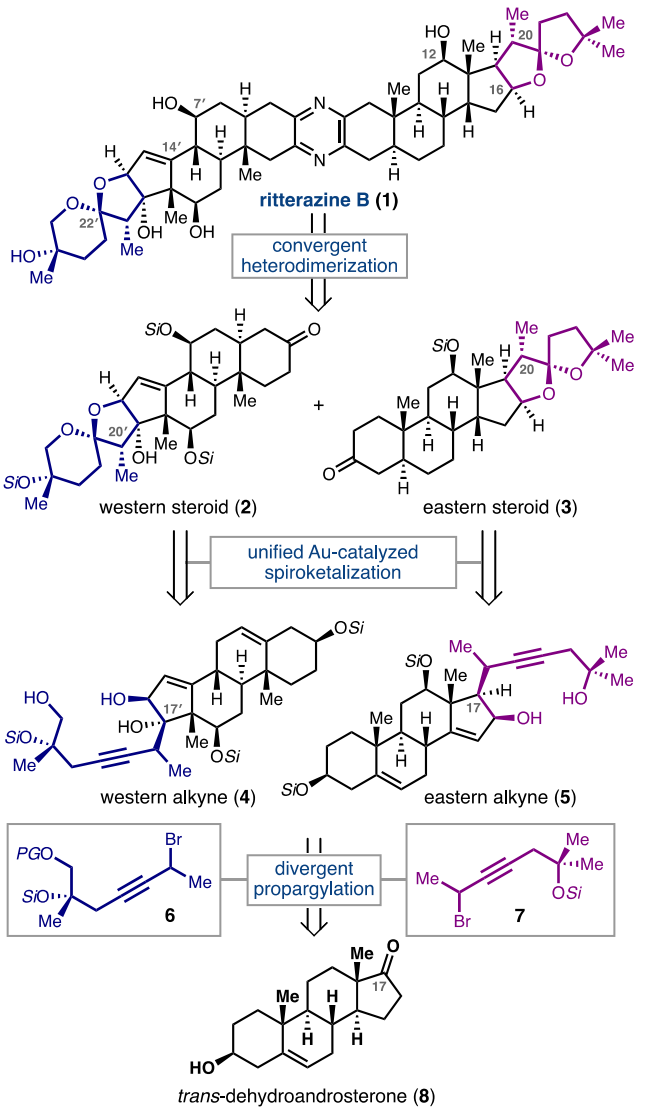


Figure 1. Retrosynthetic analysis.

C17, **13** and **14** were formed as 1:1 mixtures of epimers at C20′/C20 (*vide infra*).

While the α-stereoisomer of the C16 alcohol was crucial for imparting the desired stereocontrol in the propargylation reactions, we required the β-alcohols to elaborate to the required spiroketals. For the preparation of the western steroid (**2**), stereoinversion was accomplished by oxidation to the enone followed by cleavage of the *p*-methoxyphenyl ether[16] and hydroxyl-directed 1,2-reduction, which furnished spiroketal precursor **4** in 86% yield (Scheme 2A). After extensive experimentation,[17] treatment of diol **4** with catalytic ^{Cy}JohnPhos·AuCl (10 mol %) and $AgBF_4$ (5 mol %) provided spiroketal **15** in 68% yield as a single diastereomer.[12] To our delight, this reaction not only provided the correct configuration at the spiroketal, but also proceeded with convergence of the C20′ epimers, furnishing **15** with the required α-disposed methyl group (*vide infra*, Figure 2). The overall selectivity was found to be dependent on the choice of dichloroethane solvent, ^{Cy}JohnPhos ligand, and tetrafluoroborate counterion.

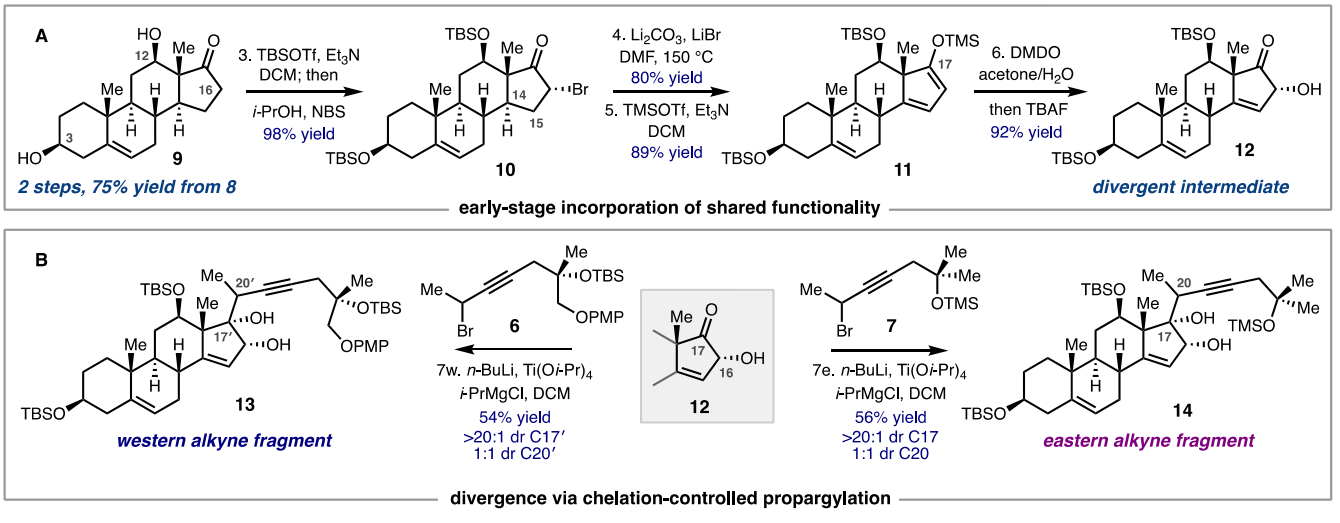
With the western spirocycle in hand, allylic oxidation of **15** at C7′ was achieved with oxochromate (**Cr(V)**).[18] To obtain the fully saturated B′ ring, the intermediate enone (not shown) was reduced with SmI_2 and 2-naphthalenethiol to furnish **16** in 85% yield as a single diastereomer; low temperatures were crucial for preventing over-reduction of the C14−C15 alkene.[17] Protection of the C7′ alcohol of **16** as the tri-*iso*-propylsilyl ether was followed by addition of $Et_3N{\cdot}3HF$ to selectively reveal the C3′ alcohol in the same pot.

Oxidation of **17** to the ketone and two-step α-bromination and azidation at C2 using procedures developed by Shair[11i] and Fuchs[11d] provided the western fragment as keto-azide **18** in 63% overall yield. The use of 1-nitropropane as solvent for the azidation instead of the traditional nitromethane was found necessary for solubilization of the intermediate bromide.[11d,i] This also significantly increased the yield by preventing undesired elimination of N_2 from **18**.

The synthesis of the eastern steroid followed a similar sequence to that described above but was modified slightly to prepare diol **5** (Scheme 2B). Following deprotection of the trimethylsilyl ether in **14** and Stahl oxidation, the C17 alcohol was removed via ketol deoxygenation with SmI_2 and H_2O.[19]

Diastereoselective 1,2-reduction was effected by treatment with di-*iso*-butylaluminum hydride to give **5**; the four-electron

Scheme 1. Preparation of the Western and Eastern Alkyne Fragments



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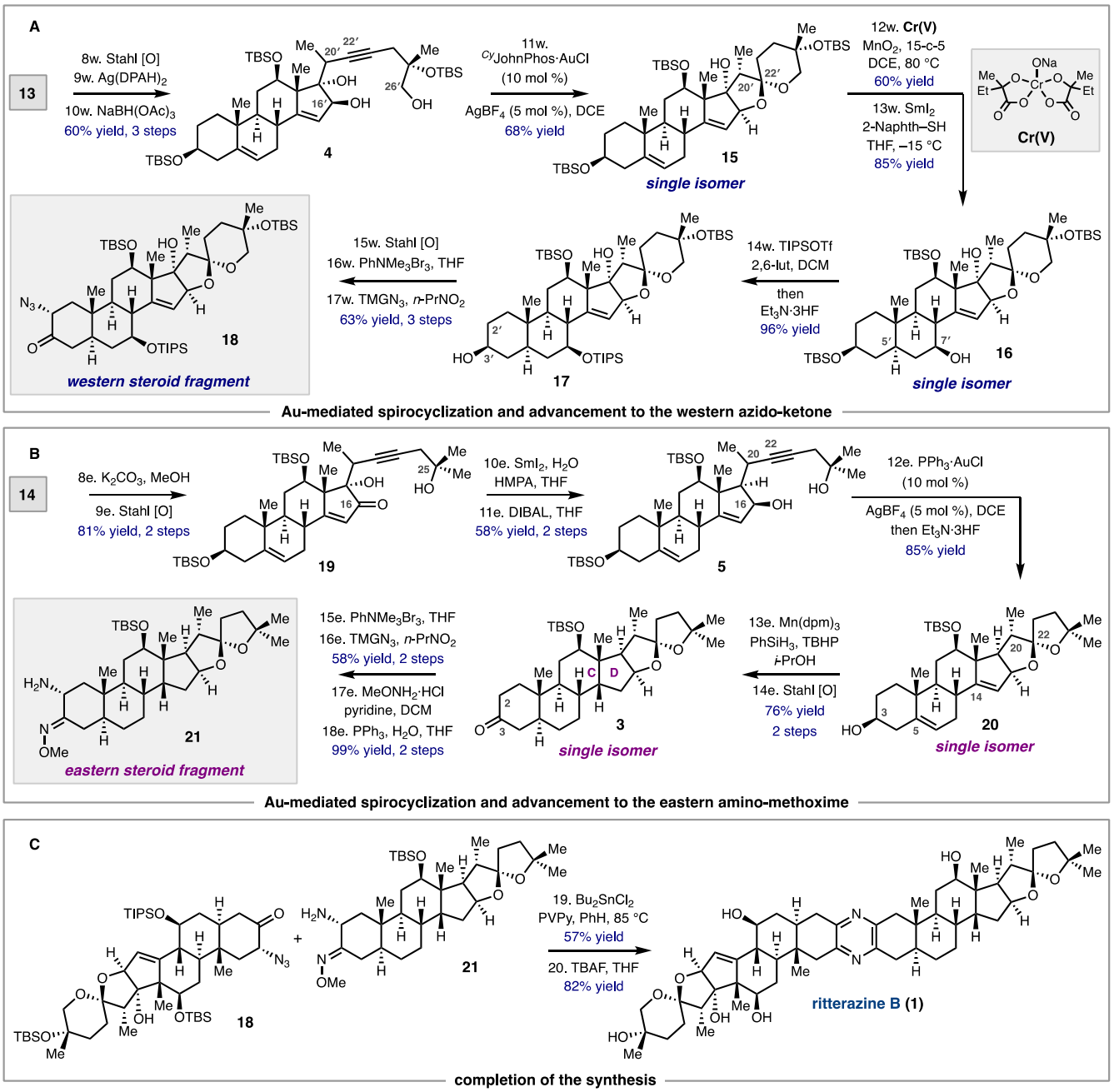
Scheme 2. Total Synthesis of Ritterazine B



reduction of **19** directly to give **5** could be accomplished with excess SmI_2, though the yield and diastereoselectivity were greatly reduced relative to the two-step procedure.

As observed for the western fragment, Au(I)-catalyzed spirocyclization proceeded smoothly to construct the 5/5 ring system, again as a single isomer. Here, it was found that direct addition of $Et_3N{\cdot}3HF$ to the reaction mixture resulted in selective deprotection of the C3 silyl ether, ultimately providing **20** in 85% yield.

The remaining two stereocenters required for the eastern fragment were installed in a single step via hydrogen atom transfer (HAT) reduction of the C5−C6 and C14−C15 alkenes under conditions developed by Shenvi and co-workers.[20] The fully saturated product was obtained with *cis*-fusion at the C/D ring-junction; DFT studies supported the thermodynamic preference for the observed stereochemistry.[17,20] This reaction proved critical for accessing late-stage material in the correct oxidation state, as typical alkene hydrogenation conditions were unable to reduce the C14−C15 double bond. To complete the eastern coupling partner, the same oxidation/bromination/azidation protocol as described for the western fragment was followed by ketone condensation with $MeONH_2{\cdot}HCl$ and Staudinger reduction[21] to furnish amino-methoxime **21** in quantitative yield.[11d]

Heterodimerization under Lewis-acid catalysis, as originally reported by Fuchs,[11d] provided the desired pyrazine (Scheme 2C). Global deprotection with TBAF[11i] delivered ritterazine B in 82% yield, representing its first total synthesis. Spectroscopic characterization data matched that reported for the natural material.[1]

The construction of each fragment hinged on the modular spiroketalization reaction. Given the observed epimerization at

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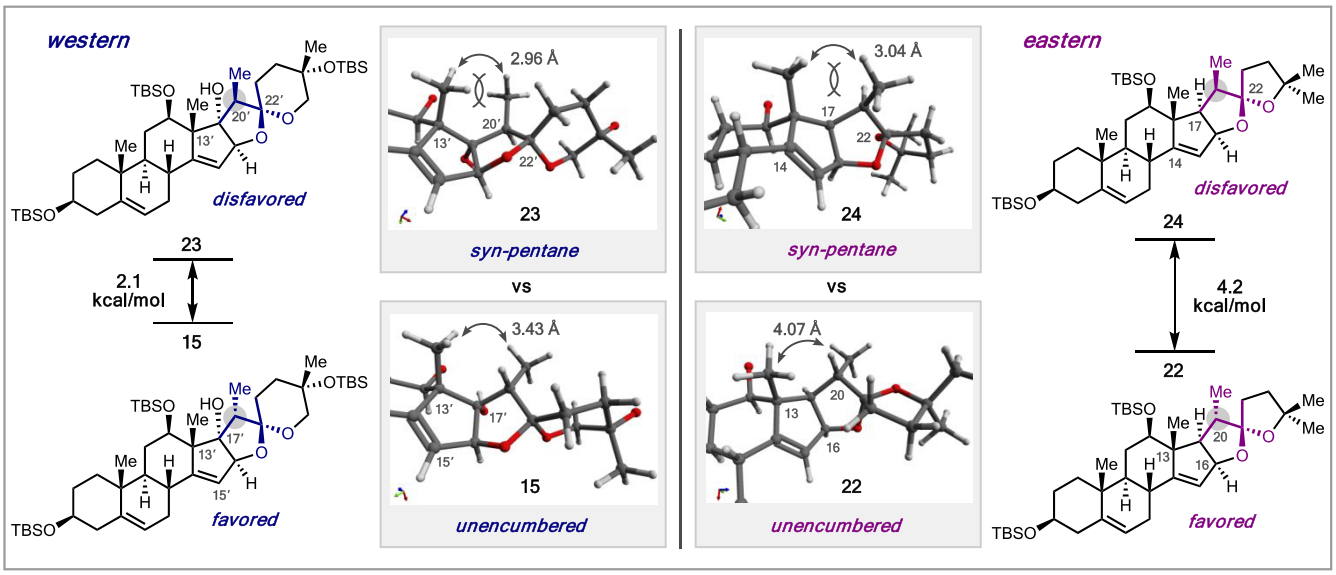

Figure 2. Thermodynamic evaluation of C20/C20′ epimers of the spiroketalization products (C12/C12′ TBS groups were removed for clarity).

C20/C20′, we hypothesize that the process occurs through an initial stereoablative monocyclization/isomerization, followed by a doubly diastereoselective ketal formation.[5,12a] To probe the preferential formation of the C20/C20′ stereocenters, ground-state energies were calculated for DFT-optimized **15** and **22** (Figure 2). Indeed, the observed isomers were found to be 2.1 and 4.2 kcal/mol lower in energy than their un-natural C20 and C20′ epimers, respectively.[22] Conformational analysis of the disfavored species **23** and **24** revealed the existence of *syn*-pentane-like interactions between the C20/C20′-β-Me and the axial C13/C13′-Me groups.[5,23] These interactions are not present with the α-disposed C20-Me groups, which appear less sterically encumbered.

In summary, the first total synthesis of ritterazine B has been completed starting from the simple steroid *trans*-dehydroandrosterone and using a unified approach to both steroid fragments. Key features of the strategy include titanium-mediated propargylations to access differentiated alkynes as well as gold-catalyzed, diastereoselective spirocyclizations to forge the spiroketals. Investigations into the biological activity of **1** and related compounds are currently underway, which will be reported in due course. It is worth noting that several multimilligram batches of these materials have been prepared thus far, and though we have elected to perform the final steps on small scale for safety, synthesis of the coupling fragments has proven to be scalable. We expect that our developed route will provide ample material for biological studies, enabling further investigation of the BSPs as anticancer therapeutics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01372.

Experimental procedures, characterization data (^{1}H and ^{13}C NMR, HRMS, FTIR) for all new compounds (PDF), coordination geometries for DFT optimized compounds

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Notes

The authors declare no competing financial interest.

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