

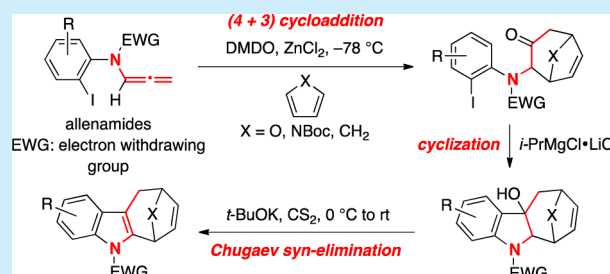
An Approach to Cyclohepta[b]indoles through an Allenamide (4 + 3) Cycloaddition–Grignard Cyclization–Chugaev Elimination Sequence

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Supporting Information

ABSTRACT: A strategy for synthesizing highly functionalized cyclohepta[b]indoles through a concise (4 + 3) cycloaddition–cyclization–elimination sequence is described. The cycloaddition features nitrogen-stabilized oxyallyl cations derived from epoxidations of *N*-aryl-*N*-sulfonyl-substituted allenamides, while the cyclization and elimination employed an intramolecular Grignard addition and a one-step Chugaev process, respectively.



Cyclohepta[b]indoles represent a prevalent structural motif among pharmaceutical entities as well as bioactive natural products such as ervitsine,¹ aristolasol,² silicine,³ ambigune E,⁴ and actinophyllic acid (Figure 1).⁵ Cyclohepta[b]indole

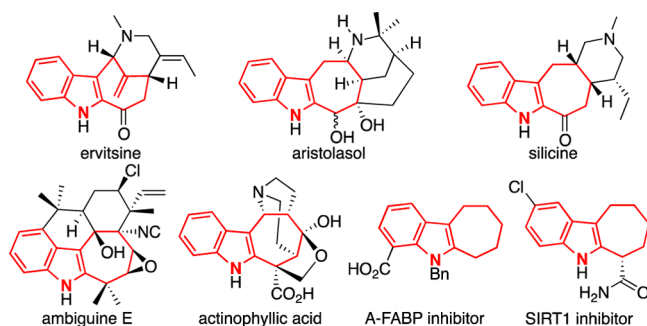
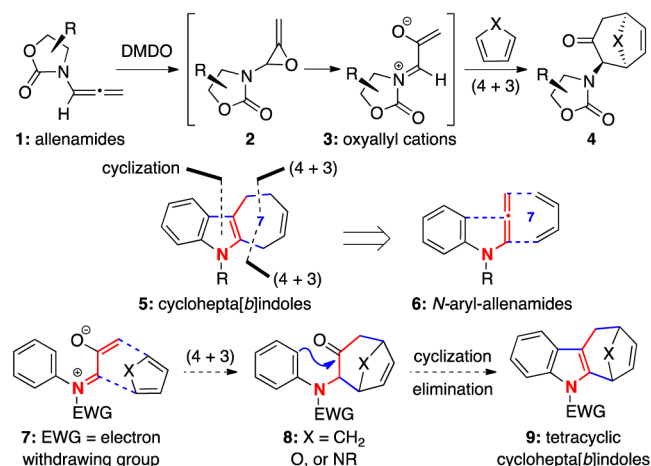


Figure 1. Representative cyclohepta[b]indole compounds.

derivatives have been shown to inhibit adipocyte fatty acid binding protein (A-FABP)⁶ and of deacetylase SIRT1.⁷ Consequently, cyclohepta[b]indoles have received much attention from the synthetic community. Previous approaches⁸ include Fischer indole syntheses,⁹ ring expansions,¹⁰ and intramolecular cyclizations.¹¹ Recently, (4 + 3) cycloaddition¹² approaches have been developed. Wu¹³ reported an elegant three-component (4 + 3) cycloaddition for constructing cyclohepta[b]indoles, while Tang¹⁴ and Iwasawa¹⁵ envisaged rhodium- and platinum-catalyzed (4 + 3) transformations. A formal (4 + 3) cycloaddition reaction was a key step in Martin's total synthesis of actinophyllic acid.¹⁶

We became interested in cyclohepta[b]indoles because of our long-standing program in (4 + 3) cycloaddition reactions¹⁷ employing nitrogen-stabilized oxyallyl cations (see 3)¹⁸ derived from epoxidations of allenamides 1 (Scheme 1).^{19–21} Structurally, only three C–C bonds separate cyclohepta[b]-

Scheme 1. (4 + 3) Cycloaddition–Cyclization Strategy

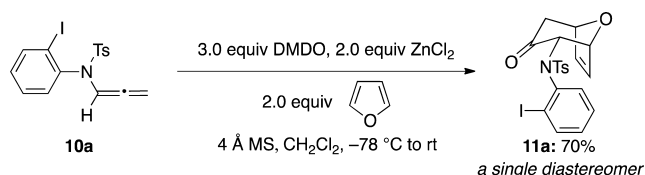


indoles 5 from *N*-aryllallenamides 6. Thus, we envisioned that while it would be difficult to include the indole formation concomitant with the (4 + 3) cycloaddition, an ensuing intramolecular cyclization from the aryl group onto the carbonyl group in (4 + 3) cycloadducts 8 should accomplish such a purpose, leading to tetracyclic cyclohepta[b]indoles 9. We wish to communicate here our success in achieving a strategy for constructing cyclohepta[b]indoles via a concise (4 + 3) cycloaddition–cyclization–elimination sequence.

Our approach toward cyclohepta[b]indoles commenced with a (4 + 3) cycloaddition reaction of *N*-aryl-*N*-sulfonyllallenamide 10a²² as shown in Scheme 2. It is noteworthy that although we have reported intramolecular (4 + 3) cycloaddition reactions of *N*-sulfonyllallenamides,²³ the current attempt represents the first

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Scheme 2. Cycloaddition of an *N*-Aryl-*N*-sulfonylallenamide

example in which an *N*-sulfonyl-substituted allenamide is used in an intermolecular (4 + 3) cycloaddition manifold. More significantly, allenamide **10a** is an *N*-aryl- or aniline-substituted allenamide. While this appears to be a minor structural perturbation from previous allenamides, it is well known that the stability and reactivity of allenamides are closely regulated by the substitution pattern on the nitrogen atom, especially when a substitution can impact on its ability to delocalize or donate toward the allenic motif.^{19,24} This constitutes the first challenge in our strategy because an *N*-aryl group allows the delocalization of the nitrogen lone pair, thereby deactivating the allenamide reactivity. However, when *N*-aryl-*N*-sulfonylallenamide **10a** was subjected to standard conditions (ZnCl_2 , DMDO, furan, and 4 Å MS in CH_2Cl_2), it reacted successfully with furan to afford the desired cycloadduct **11a** in 70% yield as a single diastereomer (Scheme 2).

With this result in hand, the scope of (4 + 3) cycloaddition reactions of *N*-aryl-*N*-sulfonylallenamides could be explored (Figure 2). Allenamides with different substituents on the aryl

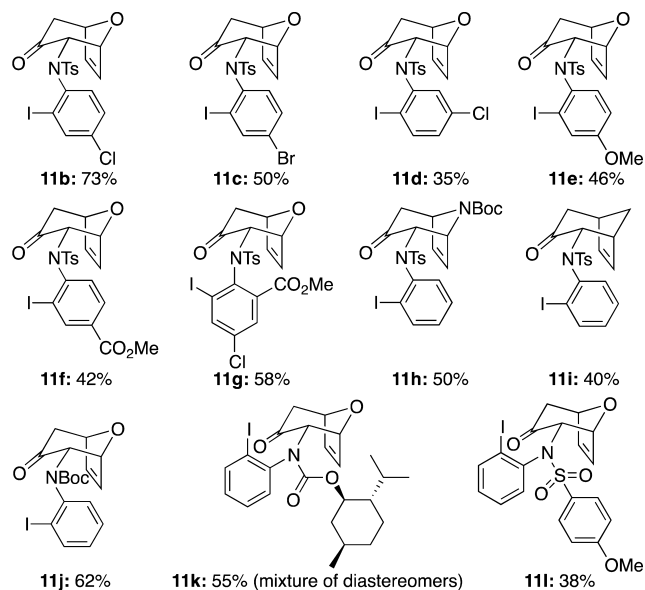
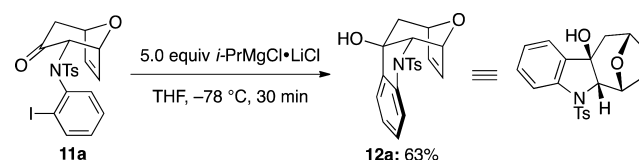


Figure 2. Scope of the (4 + 3) cycloaddition.

ring worked well to give products **11b–g** in moderate to good yields. In addition, Boc-protected pyrrole and cyclopentadiene can also serve as suitable dienes to furnish cycloadducts **11h** and **11i**, respectively. Allenamides stabilized by a carbamate group also proved to be efficient in this reaction (see **11j** and **11k**), although **11k** was obtained as an inseparable mixture with a modest 3:1 diastereomeric ratio [stereochemistry of the major isomer unassigned]. When allenamide bearing a 4-methoxybenzenesulfonyl substituent was used, the desired cycloadduct **11l** was obtained in a relatively lower yield (**11l**, 38%), thereby implying that these cycloadditions may favor allenamides with strong electron-withdrawing groups.

Having succeeded in this first step, we proceeded to complete the cyclohepta[*b*]indole ring system. As indicated above, we envisioned that an intramolecular addition of aryl anion to the carbonyl carbon should fulfill this task. To accomplish this task, we elected to go with a strategy adopted by Kobayashi and co-workers for constructing quinoline and indole rings.²⁵ By using *i*-PrMgCl·LiCl complex as the magnesium–halogen exchange reagent,^{25,26} an intramolecular Grignard addition could take place effectively to give the tetracyclic alcohol **12a** in 63% yield (Scheme 3). Other

Scheme 3. Intramolecular Grignard Addition



tetracyclic alcohols **12b–l** could also be obtained utilizing the same reaction condition as shown in Figure 3, thereby

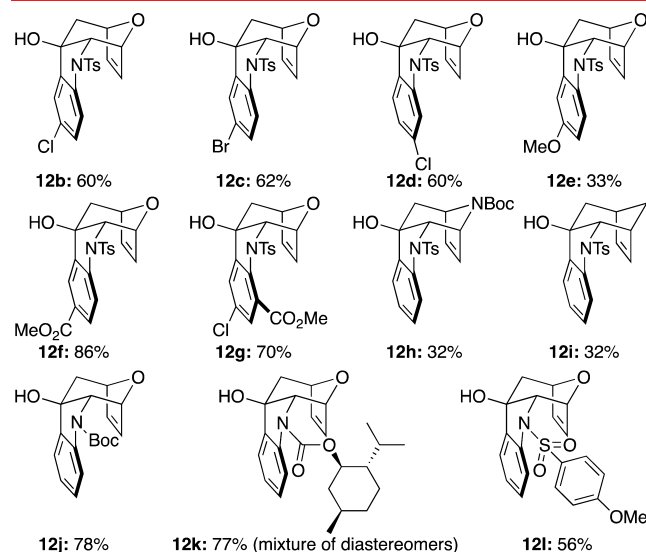
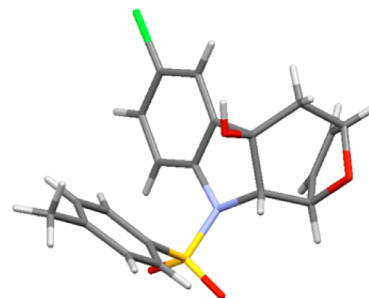


Figure 3. Intramolecular Grignard addition products.

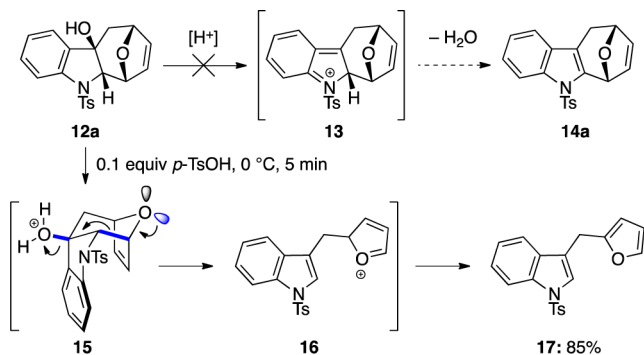
demonstrating the generality of this cyclization. The structural as well as stereochemical integrity of **12b** was unambiguously assigned through its X-ray single-crystal structure (Figure 4).

While tetracyclic alcohols **12a–l** represent highly functionalized structural manifolds with multistereogenic centers that can be useful in further transformations and evolution of

Figure 4. X-ray structure of tetracyclic alcohol **12b**.

complexity, to truly complete the indole synthesis, elimination of the tertiary alcohol should be accomplished here. We had hoped that a simple acid-induced dehydrative elimination–aromatization sequence should furnish the desired **14a** (Scheme 4). However, despite being stable to silica gel column

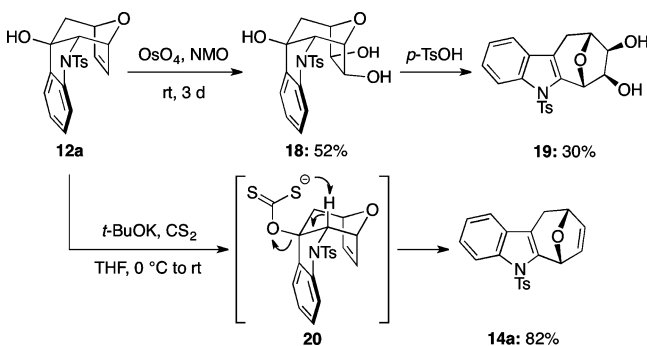
Scheme 4. Acid-Induced Grob-Type Fragmentation



chromatography, when tetracyclic alcohol **12a** was treated with catalytic amount of p -TsOH at $0\text{ }^{\circ}\text{C}$, we found complete unraveling of the tetracycle. The only product obtained was 3-furfurylindole **17**, likely derived from an acid-induced fragmentation process via intermediates **15** and **16**.²⁷

This fragmentation reaction is likely favored for two reasons: (a) The perfect *anti*-periplanar alignments between C–OH bond and the C–C bond and the C–C bond and the equatorial lone pair of the bridging oxygen (all in blue) or the perfect overlap and delocalization into the respective σ^* and (b) the formation of two aromatic systems (indole and furan) as the thermodynamic driving force. Thus, we reasoned that if we first functionalize the cycloheptenone double bond in **12a**, we should prevent the formation of furan and reduce the driving force of the fragmentation. As shown in Scheme 5, when triol

Scheme 5. Successful Eliminations



18, which could be prepared via a simple dihydroxylation from **12a**, was submitted to the same acidic condition, the elimination product **19** was obtained in 30% yield. While this result strongly supported our hypothesis and gave a highly functionalized cyclohepta[*b*]indoles in **19**, we recognized that the overall process is not as efficient.

To be more effective in completing the construction of cyclohepta[*b*]indoles, we pursued a direct elimination method via *syn*-hydrogen abstraction mechanism and hoped we could circumvent the fragmentation facilitated by the *anti*-periplanar alignments. However, SeO_2 did not react with tetracyclic alcohol **12a** under basic condition, while Burgess reagent

provided again only fragmentation product **17**. We subsequently turned our attention to transforming tetracyclic alcohol **12a** into a xanthate intermediate for a potential Chugaev's *syn*-elimination. When **12a** was treated with base and CS_2 , the desired cyclohepta[*b*]indole **14a** was obtained directly without the isolation of any xanthate intermediates (Scheme 5). This result could be explained by a direct intramolecular hydrogen abstraction of the xanthate anion **20**. It is noteworthy that base played an important role in this elimination reaction. While using t -BuOK led to 100% conversion, KH could only provide a conversion of 70%, and conversions were less than 10% when employing NaH and LiHMDS.

We subsequently applied this effective one-step Chugaev elimination to other tetracyclic alcohols **12b–l** (Figure 5). This

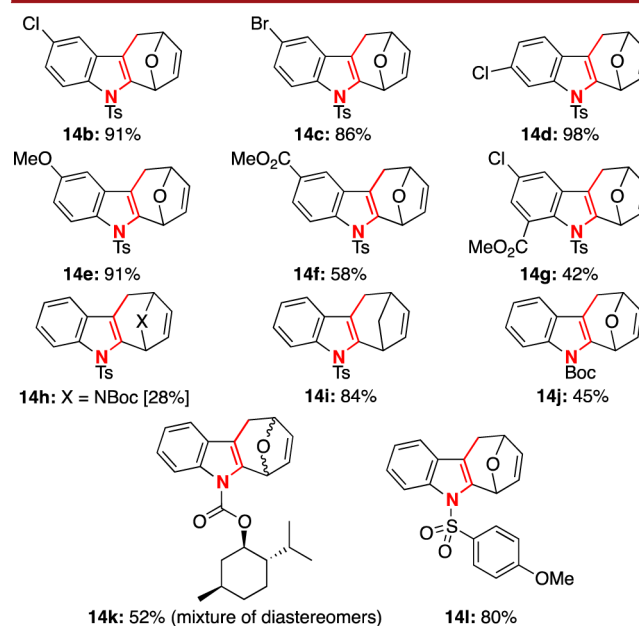


Figure 5. Synthetic scope of cyclohepta[*b*]indoles.

reaction in general gave excellent yields to afford an array of cyclohepta[*b*]indoles **14b–e,i,l**. Cyclohepta[*b*]indoles **14f** and **14g** could be obtained only when using KH as the base because t -BuOK-induced methyl ester hydrolysis in these two examples. Cyclohepta[*b*]indole **14h** was also prepared under the KH conditions since t -BuOK led to complete decomposition of the corresponding starting material **12h**; we are not clear of the rationale at this point. In addition, cyclohepta[*b*]indoles **14j** and **14k** with indole nitrogen protected as carbamates were obtained with slightly lower yields. These last three examples suggest that the *N*-protecting groups could be important in this elimination process.

We have developed a strategy for synthesizing highly functionalized cyclohepta[*b*]indoles through an efficient sequence of a (4 + 3) cycloaddition–cyclization–elimination. The cycloaddition features nitrogen-stabilized oxyallyl cations derived from epoxidations of *N*-aryl-*N*-sulfonyl-substituted allenamides, while the cyclization and elimination employed an intramolecular Grignard addition and a useful one-step Chugaev process, respectively. Applications of this strategy in natural product synthesis are currently underway.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (26) We found that a quick addition of *i*-PrMgCl-LiCl complex is crucial for achieving a good conversion. The addition of *i*-PrMgCl-LiCl THF solution should be conducted within 1 s, or all in one shot. Low conversions were found (<20%) when *i*-PrMgCl-LiCl was added dropwise via syringe pump during a period of 30 min. Prolonging the reaction time, raising the reaction temperature, or adding starting materials into *i*-PrMgCl-LiCl solution did not help improve the conversion.
- (27) When employing acids such as CSA, CF₃CO₂H, or PPTS, we obtained the same fragmentation product.