Synthetic Methods

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An Unusual Ring-Contraction/Rearrangement Sequence for Making Functionalized Di- and Triquinanes**

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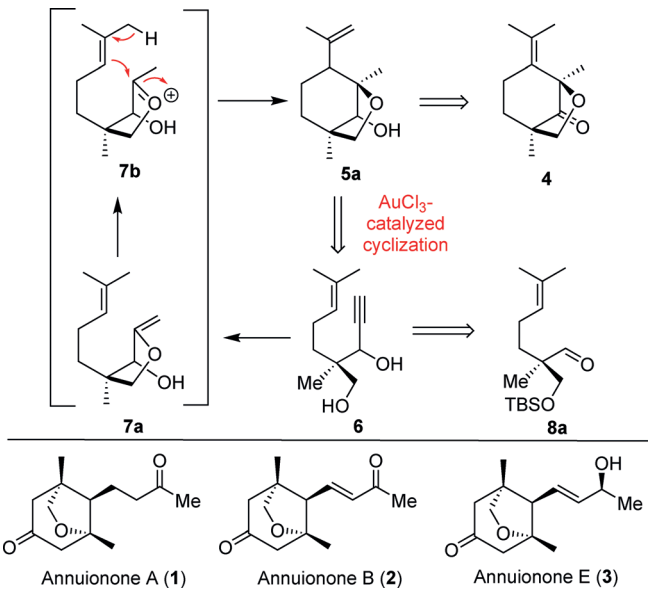
Dedicated to Professor Ganesh Pandey on the occasion of his 60th birthday

Abstract: *A novel ring contraction/rearrangement sequence leading to functionalized 2,8-oxymethano-bridged di- and triquinane compounds is observed in the reaction of various substituted 1-methyl-4-isopropenyl-6-oxabicylo[3.2.1]octan-8-ones with Lewis acids. The reaction is novel and is unprecedented for the synthesis of di- and triquinane frameworks.*

Creating molecular complexity from simple molecules is of great significance in organic synthesis.[1] Molecular rearrangements hold a special place in the formation of unusual carbon–carbon and carbon–heteroatom bond-forming reactions. Some rearrangements, whether engineered or observed serendipitously, have played significant roles in designing novel molecular architectures, including the synthesis of natural products and their analogues.[2] Synthesis of di- and triquinanes is one of the classics in organic synthesis and a number of strategies were developed for the synthesis of di- and triquinane compounds, which include ring-expansion/rearrangement and ring-contraction/rearrangement sequences.[3] During the course of the synthesis of the natural products annuionones A, B, and E (**1**–**3**; see Scheme 1), which possess a 6-oxabicyclo[3.2.1]octane framework, we encountered an unusual ring-contraction/rearrangement sequence leading to functionalized di- and triquinane frameworks, and is the subject of this communication.

In our investigations on the total synthesis of **1**–**3** and their analogues, we required an efficient synthesis of the substituted 6-oxabicyclo[3.2.1]octan-8-one **4** in an enantioselective fashion (Scheme 1). We anticipated the synthesis of **4** from the corresponding 1,5-dimethyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-ol (**5a**) by the oxidation of the alcohol and olefin isomerization. Formation of **5a** was envisaged by a gold-mediated reaction sequence involving the 5-*exo*-dig intramolecular hydroalkoxylation of the primary alcohol in the functionalized alkynol **6** to give the exocyclic enol ether intermediate **7a**, isomerization of **7a** to the oxocarbenium ion **7b**, and an intramolecular ene reaction of the alkene in **7b** with the oxocarbenium ion.[4] Synthesis of the required **6** was planned to arise from the addition of alkynyl Grignard/lithium reagents to the aldehyde **8a**, the synthesis of which starts with geraniol as established by the group of Yamamoto[5] (Scheme 1).

At the outset, a series of propargyl alcohols (**9a**–**i**) were synthesized from the enantiopure silyloxy aldehyde **8a** by the addition of alkynyl lithium/Grignard reagents (Scheme 2).[6] $AuCl_3$-catalyzed reaction of **9a**–**i** cleanly furnished the 1-methyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-ols **5a**–**i**, with various substitutions at the 5-position, in 81–93% yield. Oxidation of **5a**–**i** afforded the corresponding 5-substituted 1-methyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-ones **10a**–**i** in excellent yields. By using the same synthetic sequence, the 1-methyl-4-(1-phenylvinyl)-6-oxabicyclo-[3.2.1]octan-8-ones (±)-**10j** and (±)-**10k**, with methyl and pentenyl substitution at the 5-position, were synthesized from the aldehyde (±)-**8b** in good yields. Interestingly, the quaternary carbon center present in the substrates **9a**–**k** is essential for $AuCl_3$-catalyzed formation of the substituted 1-methyl-6-oxabicyclo[3.2.1]octan-8-ols **5a**–**k**. The structurally similar compound **9l**, which lacks the quaternary carbon center, produced an unidentifiable mixture of products in the reaction with $AuCl_3$ (Scheme 3).



Scheme 1. Retrosynthesis for 1,5-dimethyl-4-isopropenyl-6-oxabicyclo-[3.2.1]octan-8-ol by gold-catalyzed cyclization.

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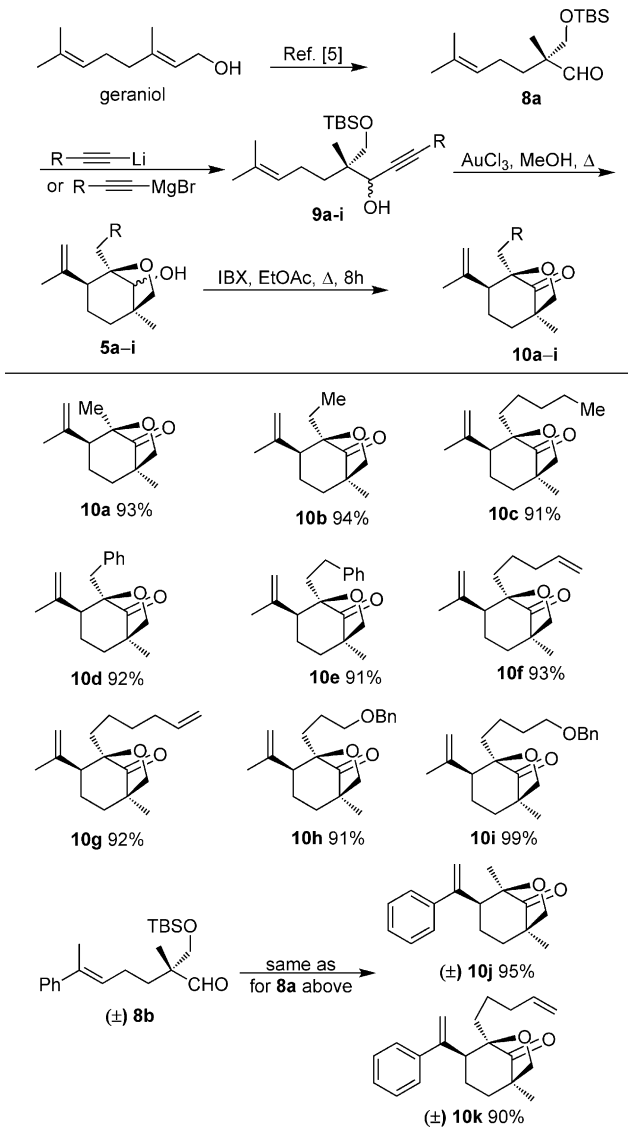
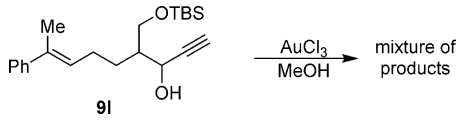
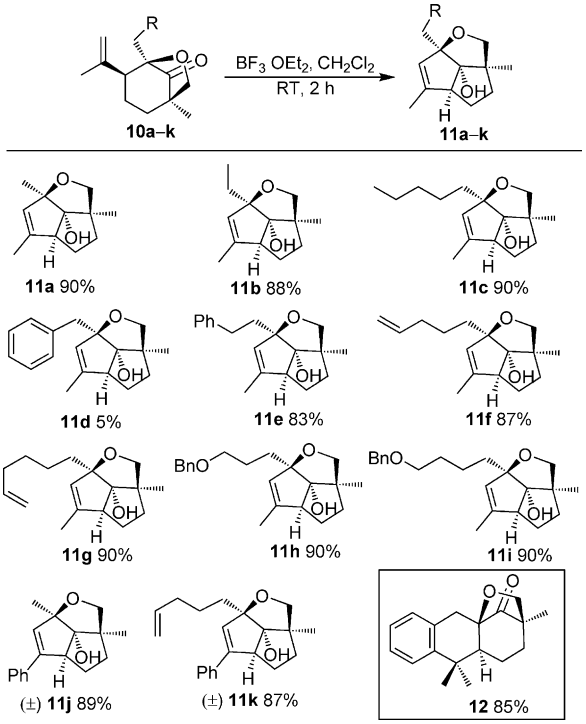


Scheme 2. Synthesis of various substituted 1-methyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-ones (**10a–k**). IBX = 2-iodoxybenzoic acid, TBS = *tert*-butyldimethylsilyl.



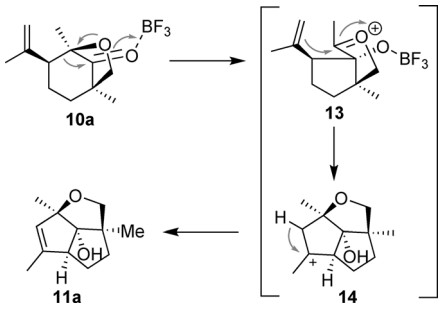
Scheme 3. Reaction of **9l** with $AuCl_3$.

After the successful synthesis of **10a–i**, acid-mediated isomerization of the exocyclic double bond of the isopropenyl group present in **10a–i** was attempted. Initial reaction of **10a** with *p*-TSA in benzene at reflux, to our surprise, furnished the 2,8-oxymethano-bridged diquinane **11a** in 55% yield. The expected product **4**, arising from the isomerization of the double bond, was not formed in the reaction. Optimization of the reaction conditions for the unusual formation of **11a** revealed that the reaction of **10a** with $BF_3{\cdot}Et_2O$ (2 equiv) furnished **11a** in 90% yield, while other Lewis acids such as $AlCl_3$, $FeCl_3$ and $TiCl_4$ also afforded the product in 79, 85, and 88% yield respectively. The structure as well as the absolute stereochemistry of **11a** was further confirmed by single-crystal X-ray structure determination.[7] The ring contraction/rearrangement reaction was found to be general and a series of structurally similar substituted 6-oxabicyclo[3.2.1]octan-8-ones (**10b–k**) furnished the corresponding 2,8-oxymethano-bridged diquinanes **11b–k** in good yields upon reaction with $BF_3{\cdot}Et_2O$ (2 equivalents; Scheme 4). However, 5-benzyl-1-methyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-one (**10d**) furnished the corresponding rearranged product **11d** in a mere 5% yield. The major product formed in the reaction was the tetracycle **12**, thus resulting from the reaction of phenyl group with the isopropenyl olefin.



Scheme 4. $BF_3{\cdot}Et_2O$-mediated rearrangement of substituted 6-oxabicyclo[3.2.1]octan-8-ones **10a–k** to the 2,8-oxymethano-bridged diquinanes **11a–k**.

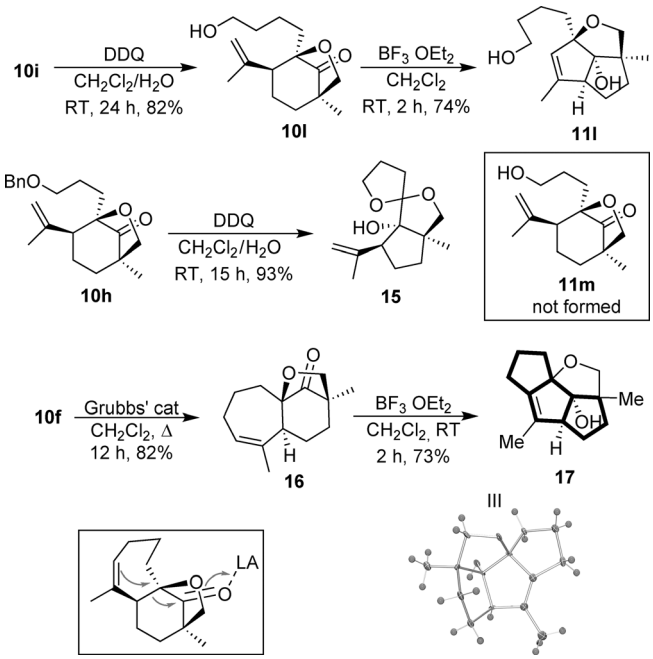
The ring contraction/rearrangement reaction of simple cyclohexanones mediated by Lewis acids is not common,[8] whereas ring-contraction reactions such as the Favorskii rearrangement[9] and the α-ketol rearrangement[10] involving α-halo ketones and α-hydroxy ketones, respectively, are well documented. We were intrigued by the rearrangement and envisaged that the driving force for this reaction is the stabilization of the incipient carbocation, formed during the ring-contraction step, by the heteroatom (in this case oxygen) in the form of the oxocarbenium ion **13** (Scheme 5), similar to that observed in α-ketol rearrangements. Thus, formation of the product can be explained by the following mechanism. Activation of the carbonyl group in **10a** by the Lewis acid with subsequent ring contraction leads to the oxocarbenium ion **13**, which undergoes concomitant ene-type reaction with



Scheme 5. Proposed mechanism for the formation of **11a**.

the isopropenyl group to form of **14** and affords the 2,8-oxymethano-bridged diquinane **11a**.

To get further insight into the mechanism of the reaction, the following reactions were performed. The substituted 6-oxabicyclo[3.2.1]octan-8-one **10l**, possessing a hydroxybutyl substitution at the 5-position and capable of intercepting the intermediate oxocarbenium ion, was synthesized and subjected to the reaction with $BF_3{\cdot}Et_2O$ (Scheme 6). Interestingly, the reaction afforded the corresponding **11l** in 74% yield. It was anticipated that the formation of medium-sized rings would be difficult, and hence the reaction of **11m**, having hydroxypropyl substitution at the 5-position, would be ideal for intercepting the oxocarbenium ion **13**.[11] However, attempted debenzylation of the benzyl ether in **10h** itself directly afforded the ketal **15**, which results from the interception of **13** with the free hydroxy group, in excellent yield and further corroborates the suggested mechanistic pathway. In an extension of the methodology to the synthesis



Scheme 6. Synthesis of the oxymethano-bridged triquinane **17**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

of an oxymethano-bridged triquinane, the substrate **16** (prepared from **10f**) was subjected to reaction with $BF_3{\cdot}OEt_2$. We were pleased to find that the ring contraction/rearrangement sequence proceeded smoothly and the oxymethano-bridged triquinane **17** was obtained in 73% yield. Stereochemistry of the newly formed stereogenic centers in **17** was further confirmed by X-ray crystal structure analysis.[12]

The oxymethano-bridged diquinanes represent the ABE ring system of the structurally related pentacyclic diterpenoid natural product ryanodol (**18**; Figure 1).[13]

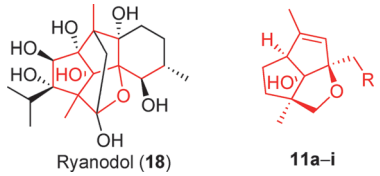


Figure 1. Pentacyclic diterpenoid natural product ryanodol.

In conclusion, an unprecedented ring contraction/rearrangement reaction was observed in the reaction of various substituted 1-methyl-4-isopropenyl-6-oxabicyclo[3.2.1]octan-8-ones with a Lewis acid to furnish functionalized 2,8-oxymethano-bridged diquinanes. The generality of the reaction was further showcased in the synthesis of a structurally complex oxymethano-bridged triquinane.

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[6] No efforts were made to estimate the diastereomeric ratio of the alcohols **9a**–**k**, as it is of no consequence in the oxidation to the ketones **10a**–**k**.

[7] CCDC 993976 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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