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CATION INDUCED REARRANGEMENT OF 8-AZABICYCLO[3.2.1]OCTA-2,6-DIENES TO 6-AZABICYCLO[3.2.1]OCT-2-ENES

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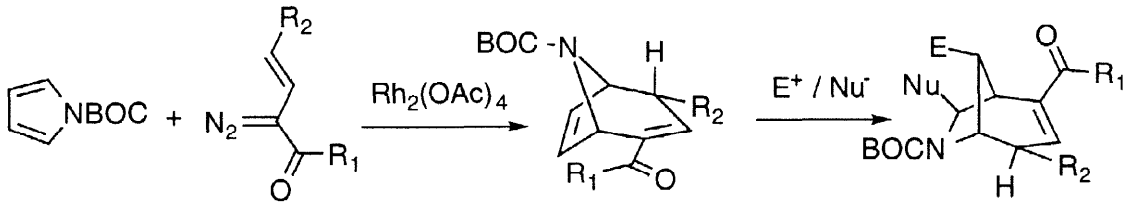
Abstract: Various electrophiles induce the rearrangement of 8-azabicyclo[3.2.1]octa-2,6-dienes to 6-azabicyclo [3.2.1]oct-2-enes.

Azabicyclic systems have been extensively used in recent years as key structural components of various pharmaceutical agents. Consequently, flexible methods for the construction of azabicycles are of considerable interest. We have recently described a very general method for the construction of tropanes by a [3 + 4] annulation between rhodium-stabilized vinylcarbenoids and pyrroles.[1] This chemistry has been applied to the synthesis of novel dopamine and serotonin reuptake inhibitors.[2] Another bicyclic system worthy of development is the 6-azabicyclo[3.2.1]octane system. Several natural products contain this bicyclic core structure, and various biologically active analogs have been prepared.[3-5] In this paper we describe a direct and flexible entry to the 6-azabicyclo[3.2.1]octanes by a facile cation induced rearrangement of the 8-azabicyclo[3.2.1]octa-2,6-dienes, which are readily derived from [3 + 4] annulations[1] between rhodium-stabilized vinylcarbenoids and pyrroles (Scheme 1).

Scheme 1



The synthesis of tropanes with unsaturation at the C2,3 and C6,7 positions is readily achieved using the published [3 + 4] annulation procedure.[1] Even though the selective hydrogenation of the C6,7-double bond of these tropanes is well established,[1b] attempts at functionalizing the C6,7-position by other electrophilic additions led to the discovery of the facile rearrangement of the tropanes to the 6-azabicyclo[3.2.1]oct-2-enes (Scheme 2).

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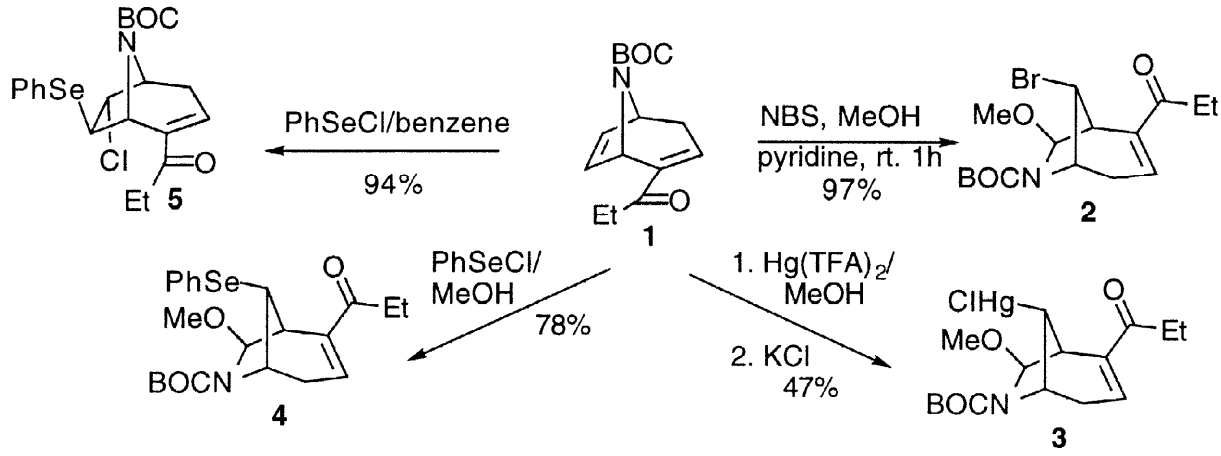
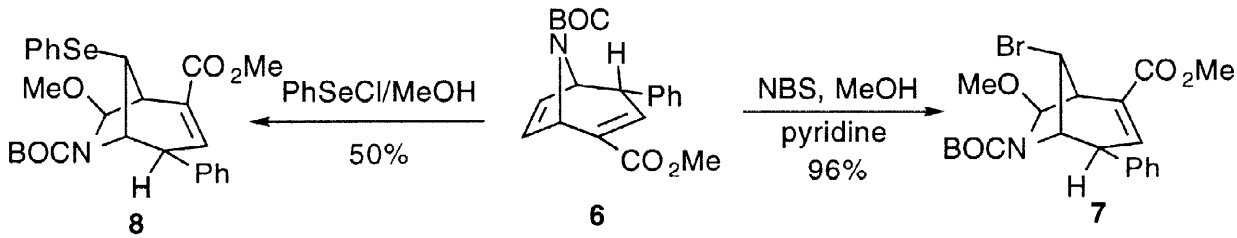
Reaction of the tropane **1** with NBS in the presence of methanol and pyridine resulted in the formation of the 6-azabicyclo[3.2.1]oct-2-ene **2** in 97% yield.[6] A similar rearrangement was observed in the reaction of **1** with mercuric trifluoroacetate resulting in the formation of **3** in 47% yield. Likewise the reaction of **1** with phenylselenenyl chloride generated **4** in 78% yield. The solvent has a major role in the outcome of these reactions as the reaction of **1** with phenylselenenyl chloride in a non polar solvent such as benzene resulted in the formation of the unrearranged tropane **5** in 94% yield. Reaction with weaker electrophiles such as mercuric acetate or palladium acetate led to recovered starting material while the reaction of **1** with protic acids formed uncharacterizable products.

Scheme 2



The issue of stereocontrol in these transformations was explored in the case of the 4-phenyl tropane derivative **6** (Scheme 3). Reaction of **6** with NBS in methanol/pyridine resulted in the formation of the 6-azabicyclo[3.2.1]oct-2-ene **7** as a single diastereomer in 96% yield. The *exo* stereochemistry for the phenyl group in **7** was readily ascertained by the distinctive lack of coupling between the proton at C-4 and the bridgehead proton.[7] Furthermore, the lack of coupling for the C-8 proton is also very characteristic[7] and shows that the electrophile is positioned on the side of the aza-bridge. A similar reaction was possible with phenylselenenyl chloride in methanol leading to the formation of **8** in 50% yield.

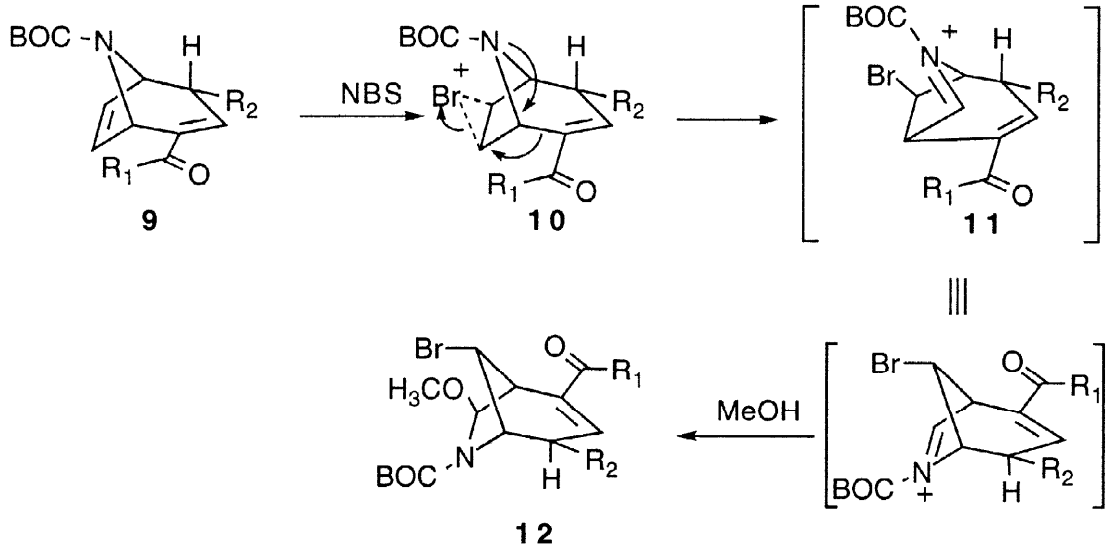
Scheme 3



A reasonable mechanism for the conversion of the tropane to the 6-azabicyclic system is illustrated for the NBS reaction in Scheme 4. Electrophilic attack of the tropane **9** from the β face forms the bromonium ion **10** which undergoes a 1,2 shift of the vinyl group to form **11**. Capture of **11** by methanol would generate the 6-

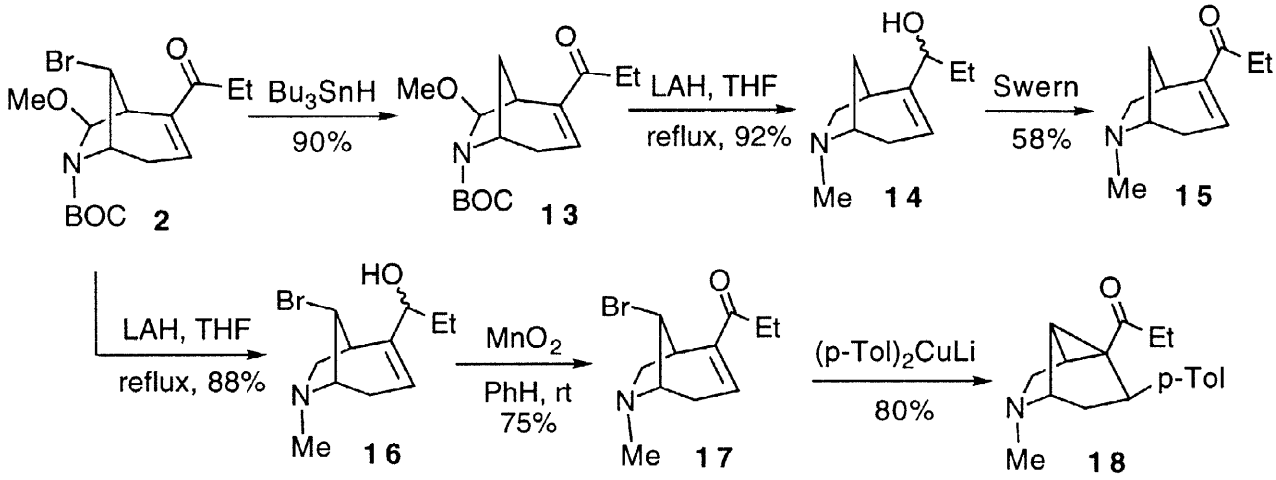
azabicyclic system **12**. The observed stereochemistry is fully consistent with this mechanism. Related cation induced rearrangements have been observed in azabicyclic systems,[3h-n] but the rearrangements are rarely as clean as the ones described herein. A complimentary free radical induced rearrangement of tropanes to 6-azabicyclo[3.2.1]octanes has been recently reported by Rigby and Pigge.[3i,j]

Scheme 4



Further transformations on the azabicyclic compounds are readily achieved as illustrated in Scheme 5. Tributyltin hydride induced debromination of **2** generated **13**, which on treatment with lithium aluminum hydride followed by Swern oxidation generated the unsaturated ketone **15**. Alternatively, **2** can be converted to the bromo derivative **17** by successive lithium aluminum hydride reduction and manganese dioxide oxidation. Cuprate addition to **17** resulted in an intramolecular nucleophilic substitution by the intermediate enolate, leading to the formation of the novel tricyclic structure **18**.

Scheme 5



In summary, 6-azabicyclo[3.2.1]oct-2-enes are readily obtained by cation induced rearrangement of 8-azabicylo[3.2.1]octa-2,6-dienes. This rearrangement expands the synthetic utility of the 3 + 4 annulation between vinylcarbenoids and pyrroles. The utilization of these 6-azabicyclic compounds as precursors to biologically active analogs is in progress.

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