Aza-Terpenes: Synthesis of Aza-Tricyclene and Aza-Pinene Stereoisomers as Potential Inhibitors of Monoterpene Synthases

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The biosynthesis of the vast majority of naturally occurring cyclic monoterpenes is proposed to proceed through the α-terpenyl cation **1**. Intramolecular Markovnikov addition to the cyclohexenyl double bond of **1** leads to pinyl cation **2**, which represents the pinane skeleton. Wagner-Meerwein rearrangement of cation **2** gives rise to either a fenchyl cation (fenchane skeleton) or bornyl cation **3** (bornane skeleton), depending on how this rearrangement takes place. Alternatively, the bornyl cation **3** could also be generated *via* an anti-Markovnikov electrophilic addition to the cyclohexenyl double bond of **1**. Wagner-Meerwein rearrangement of cation **3** generates the camphyl cation **4**. The unusual tricyclene skeleton is formed from either **3** or **4** (or its non-classical carbonium ion **5**) through the loss of H-6.

The stereospecific synthesis of 1-aza-pinene, 1-aza-tricyclane and 2-aza-tricyclane, all potential inhibitors of monoterpene synthases, is presented starting from inexpensive and enantiomerically pure starting materials.