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A SUBSTRATE-DIRECTED SYNTHESIS OF SUBSTITUTED 2-AZAADAMANTANES

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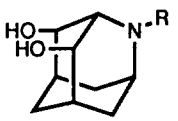
ABSTRACT: A synthesis of mono- and disubstituted 2-azaadamantanes with control of substituent stereochemistry has been developed.

Because of its unique and well defined molecular architecture, adamantanes have served not only as synthetic novelties, but also as tools in physical organic chemistry and biology.[1] Recent reports on the chemistry of heteroadamantanes and other caged molecules[2] and a heightened interest in their potential applications led us to examine the synthetic accessibility of specifically substituted 2-azaadamantanes.[3] In this letter, we wish to report the efficient synthesis of three isomeric nonbridgehead disubstituted 2-azaadamantanes **1**-**3** as well as the nonbridgehead monosubstituted system **4**, with control of substituent stereochemistry.



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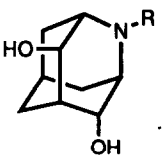

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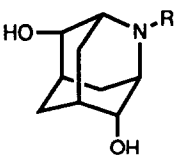

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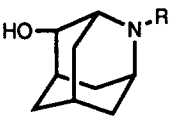


4

Previous work in the construction of these molecules has focused primarily on the nonselective addition of electrophiles to electron rich bicyclo[3.3.1]nonane derivatives.[4] Despite their poor yields, these procedures have remained the methods of choice for 2-azaadamantane synthesis. A procedure developed in these laboratories[5] differed fundamentally from former approaches by reversing the role of the reacting partners (an umpolung), using the bicyclic system as the electrophile. In an extension of this new approach, we have added the flexibility required for the synthesis of isomeric compounds, all of which derive from a common intermediate **5**.

Bicyclic ketone **5**, readily available from 2-adamantanone,[6] reacted cleanly and regioselectively with NBS, yielding only the 4-*exo*-bromide (Scheme). Hydrolysis and epoxidation

at elevated temperatures (mCPBA + radical inhibitor)[7] afforded **6** in 80% yield (for three steps). Transannular cyclization was effected in one step by reductive amination of **6** (RNH_2, HOAc, $NaBH_3CN$), giving good yields of *anti*-diols **1**.[8,9]

Systems **2** and **3** were also accessed through ketone **5**. Conversion of **5** to its tosylhydrazone followed by treatment with excess n-butyllithium provided an inseparable 55:45 mixture of dienes **7** and **8**, respectively.[10] Direct conversion of the dienes to their corresponding *exo,exo*-bis-epoxides **9** and **10**, followed by heating the mixture with excess primary amine at 120-135 °C gave good yields of *anti*-diols **2** and **3**, respectively.[5] These were easily separable on basic alumina (column or preparative TLC) and, because of symmetry characteristics, their structures readily assigned by ^{13}C-NMR.[11]

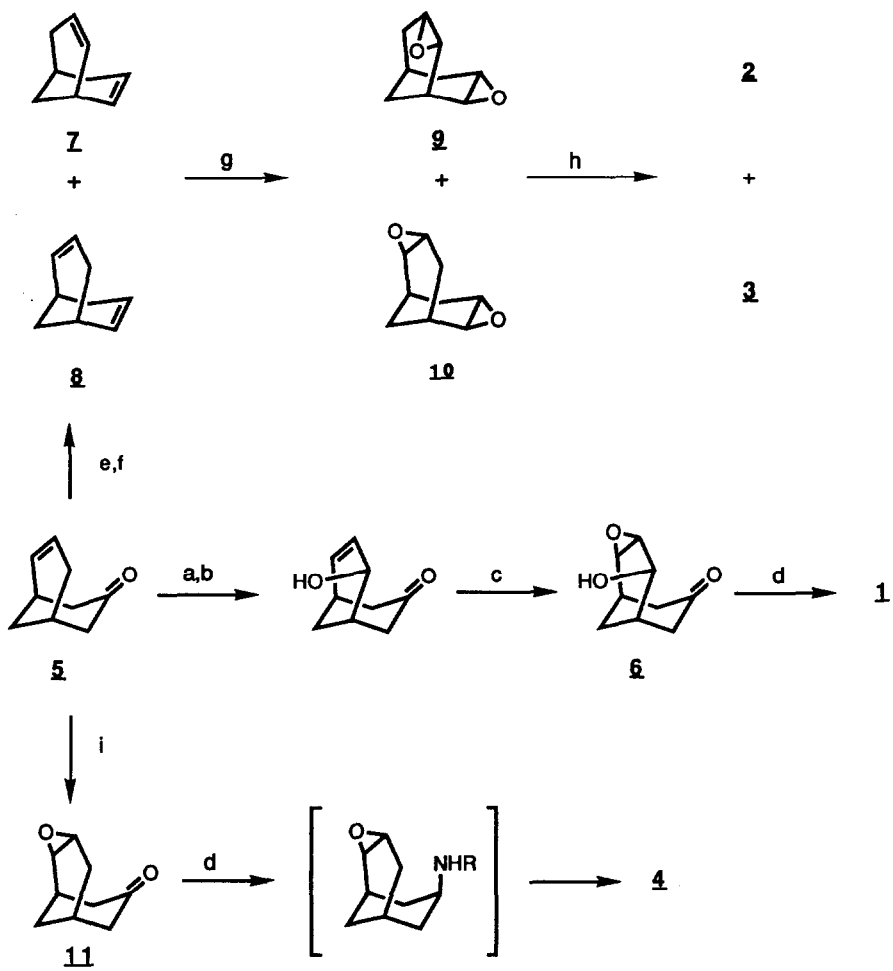
In addition to the disubstituted systems already described, 4-monosubstituted-2-azaadamantanes are also easily synthesized from **5**. For example, treatment of **5** with mCPBA followed by transannular cyclization (CH_3NH_2, $NaBH_3CN$) provided *anti*-**4** in excellent yield. We have also observed that alcohols **1**-**4** are readily chlorinated ($SOCl_2$) and reduced (LAH) to the parent azaadamantane. Further, treatment of the chloro derivatives with alkoxide gave the corresponding *anti*-ethers. The utility of **5** has also been demonstrated by its efficient conversion, in 4 steps, to the fluxional molecule barbaralane.[6]

The stereochemistry of the substituents in **1**-**4** is directed entirely by the substrate. In each case where transannular cyclization occurs, only one pathway favors ring formation--opening of the epoxide from the *endo*-face of the molecule. This is, in fact, the only observed reaction process (additionally, none of the regioisomeric protoadamantane is detected). The exclusive formation of *exo*-epoxides **6**, **9**, **10**, and **11** arises from the precedented addition of electrophiles to the *exo*-face of bicyclic molecules.[12] These cyclization substrates are thus ideally set up to yield the *anti*-substituent stereochemistry. For **1** and **4**, reduction of an intermediate imine (not isolable, from [**6** or **11**] + RNH_2, $NaBH_3CN$) under acidic conditions occurs preferentially from the *exo*-face of their cyclization precursors, conveniently providing only the *endo*-amine. In a related reaction,[13] amine mixtures were formed when the faces of a heterodiamantane intermediate were both hindered. In our case, cyclization to the 2-azaadamantane occurs spontaneously,[5,14] affording only the *anti*-hydroxy species.

The kinetic behavior of derivatives of **1**-**4** was investigated. Treatment of **1**-**4** with $SOCl_2$ gave the corresponding *anti*-chloro compounds. Each of these ß-haloethylamines is very reactive--there is a large rate enhancement for release of chloride (relative to 2-chloroadamantane). This is most likely due to anchimeric assistance by the neighboring nitrogen atom.[15] Each was also found to alkylate 4-(p-nitrobenzyl)pyridine and to possess an intrinsic reactivity approximately equal to that of mechlorethamine, as reflected by their Swain-Scott nucleophilic selectivity s constants (about 1.2 for each).[16] This suggests a rapidly formed, yet reasonably selective, alkylating reactivity for these compounds.

Because of their brevity and generality (R can be alkyl, aryl, or aminoalkyl), these methods should give ready access to a variety of new, reactive 2-azaadamantanes.

SCHEME



a) NBS, benzoyl peroxide, CCl_4, reflux 10 min. (99%); b) $NaHCO_3$, H_2O/THF, reflux (98%); c) mCPBA, 3-t-butyl-4-hydroxy-5-methylphenyl sulfide, 1,2-dichloroethane, 90 °C, 2 h. (82%); d) RNH_2, $NaBH_3CN$, HOAc, MeOH, r.t.; e) $TsNHNH_2$, H_2O/MeOH, 60 °C -> 5 °C (95%); f) 2.5 eq. nBuLi, THF, -78 °C -> r.t. (54%); g) mCPBA, CH_2Cl_2, 0 °C -> r.t. (60%); h) RNH_2, MeOH, 120-135 °C, chromatography; i) mCPBA, CH_2Cl_2, 0 °C -> r.t. (84%)

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8. Purified, isolated yields of **1** derivatives: R = H, 70%; $-CH_3$, 73%; $-nC_3H_7$, 88%; nC_6H_{13}, 55%; $-CH_2CH_2$-c-$N(CH_2)_5$, 87%.
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11. a) Examples of purified, isolated yields of **2** and **3** from cyclization of epoxide mixture [**9** + **10**]: R = $-CH_3$, **2**: 55%, **3**: 23%; R = $-CH_2CH_2$-c-$N(CH_2)_5$, **2**: 46%, **3**: 38%. b) All new compounds have been fully characterized spectrally and satisfactory elemental composition established by either combustion analysis or high resolution mass spectrometry.
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