

AN N-ACYLIMINIUM ROUTE TO THE 8-AZABICYCLO[3.2.1]OCTANE (TROPANE)
AND THE 9-AZABICYCLO[4.2.1]NONANE RING SYSTEM
SYNTHESIS OF (±)-ANATOXIN-A

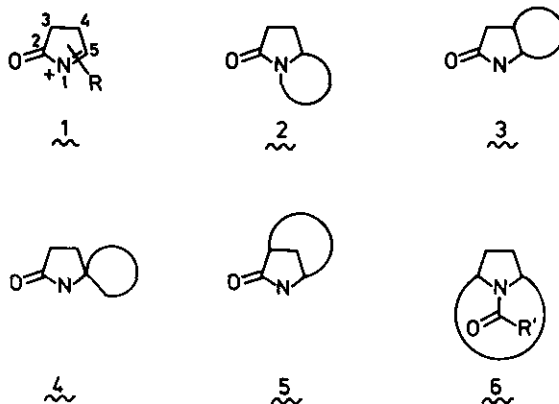
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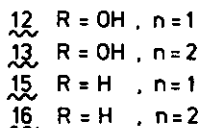
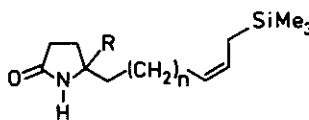
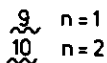
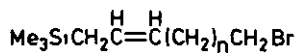
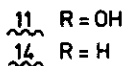
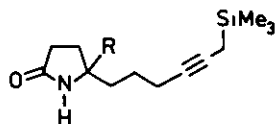
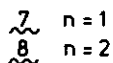
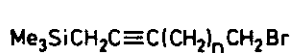
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Abstract - Propargyl and allyl silanes 20-22, readily prepared from succinimide, cyclize on dissolution in formic acid to azabicycles 23-25 in excellent yields.

Intramolecular reactions of N-acyliminium intermediates 1, readily obtainable from succinimide, have proven to be eminently useful for the synthesis of azabicyclic compounds¹. If the substituent R is a chain, containing a suitable and properly located nucleophilic carbon atom, either of the molecules 2-5 can be prepared, dependent on the site of attachment of R. Linearly fused systems 2² and 3³ are available from 1- and 4-substituted 1, respectively. Spiro system 4 arises, if R is located at position 5⁴, and bridged system 5 is obtained, if R is at position 3⁵. In this communication we show that bridged system 6 is also easily accessible from succinimide by using N-acyliminium ion chemistry⁶. Azabicyclic 6 is the basic skeleton of pharmacologically important compounds like the tropane alkaloids⁷ and anatoxin-a⁸.

Our synthetic route to 6 began with the addition reaction of the Grignard reagents, derived from 8-10^{9,10}, to succinimide, leading to hydroxy lactams 11-13. Best

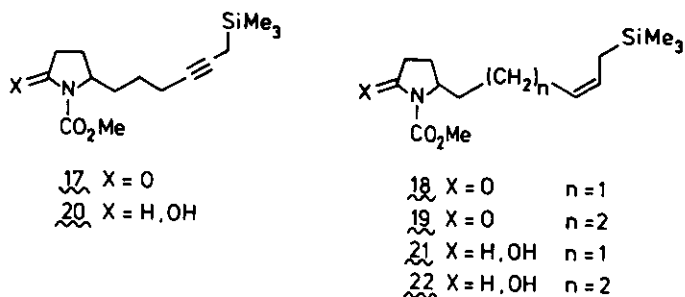




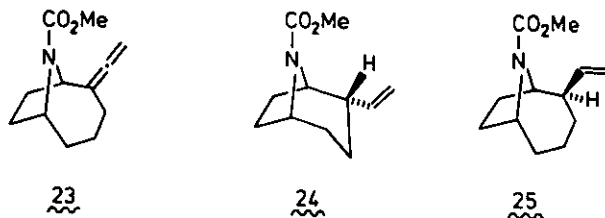
yields were obtained by using 3 eq of Grignard reagent¹¹. Alternatively, one can first employ 1 eq of MeMgCl to make the succinimide salt, followed by 2 eq of the more expensive Grignard reagent. Bromide 7^{9,10} was useless for our purposes, since all attempts to prepare its Grignard reagent failed. The crude hydroxy lactams 11-13 were not purified, but immediately reduced with NaBH₃CN in acetic acid¹² to pyrrolidones 14-16¹⁰. The overall yield of pure pyrrolidone was about 60% from succinimide.

Having established the first carbon-carbon bond by a Grignard reaction, the second carbon-carbon bond was thought to arise from an N-acyliminium cyclization reaction. We have found earlier that the allyl- and propargylsilane moieties are excellent nucleophiles for this reaction type^{2c,5b}. To arrive at the required N-acyliminium ion, the methoxycarbonyl group was attached to the nitrogen. Best results were obtained by reaction of the lithium salts 14-16 (generated by using 1.1 eq of lithium diisopropylamide in THF at -78°C) with methyl cyanoformate¹³, furnishing 17-19¹⁰ in about 90% yield. Ethyl chloroformate appeared to be a very poor reagent for this purpose, giving a substantial amount of O-acylation. Reduction of 17-19, by using the pH-controlled NaBH₄ method¹⁴ in ethanol at -20°C cleanly gave reaction of the ring carbonyl group to furnish hydroxy carbamates 20-22 in nearly quantitative yield. Higher reduction temperatures led to by-products resulting from ring opening and overreduction.

Ring closures of 20-22 were readily effected by dissolution in formic acid at room temperature. Propargylsilane 20 led to allene 23¹⁰ in 70% overall yield from 17.



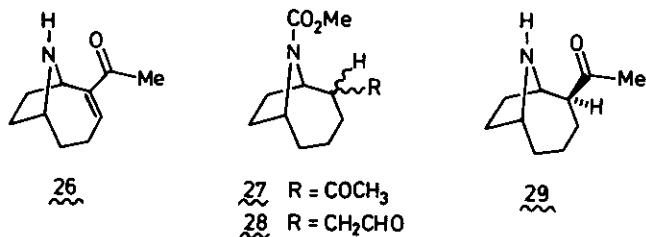
The allenic structure was immediately apparent from the typical IR (1955 cm^{-1}) and ^{13}C NMR absorptions (δ 204.5 and 204.1, 106.9 and 106.3, 75.0; most carbon atoms showed two peaks due to hindered rotation). Allylsilane $\underline{21}$ afforded olefin $\underline{24}$ ^{10,15} as a single stereoisomer in 75% overall yield from $\underline{18}$. The preference for formation of a six-membered ring with an equatorial vinyl group has been observed previously in related cyclization reactions^{2c,5b}. Allylsilane $\underline{22}$ gave olefin $\underline{25}$ ^{10,15} in addition to a small amount of its stereoisomer (ratio 19:1) in 73% overall yield from $\underline{19}$.



The cyclization products $\underline{23}$ - $\underline{25}$ were obtained in clean, fast and irreversible reactions. These reaction characteristics are on the one side a consequence of the favorable nucleophilic properties of allyl- and propargylsilanes, and on the other hand due to the high electrophilicity of N-acyliminium ions¹⁶. The methodology presented here may well lead to various other ω -aza[x.y.1]bicycloalkanes, e.g. by using glutarimide and/or other nucleophilic chains as starting materials. Research in this direction is in progress.

Anatoxin-a ($\underline{26}$) is a potent neurotoxin, produced by certain strains of the fresh water blue green alga *Anabaena flos-aquae* (Lyngb.) de Bréb⁸. This rather simple alkaloid with interesting pharmacological properties¹⁷ has been synthesized both as racemate¹⁸ and as pure enantiomer^{17,19} by a number of research groups.

We herewith add a formal synthesis of racemic $\underline{26}$ starting from $\underline{25}$. Wacker oxidation²⁰ of the inseparable 19:1 mixture of $\underline{25}$ (CuCl (1 eq), PdCl_2 (0.2 eq), O_2 , DMF,



H₂O) led to ketone 27 as a 1:1 mixture of isomers in 64% in addition to 5% of aldehyde 28. Treatment of 27 with in situ generated iodotrimethylsilane (NaI, Me₃SiCl) in refluxing acetonitrile²¹ furnished (±)-dihydro-anatoxin-a as a 4:1 mixture²² of 29 and its stereoisomer²³. This completed a formal synthesis of racemic anatoxin-a, since Rapoport et al. have published¹⁷ the conversion of 29 into 26. Our synthesis of the isomer mixture of 29 comprises 6 steps (23% overall) from succinimide and 10 steps (7% overall) from the THP-ether of 4-pentyn-1-ol^{8,2c}.

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23. The yield of crude but virtually pure (NMR) dihydroanatoxin-a was 95%. Spectral data were identical to those published by Rapoport et al^{19b}.

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