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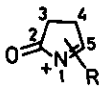
Abstract - Propargyl and allyl silanes 20-22, readily prepared from succinimide, cyclize on dissolution in formid acid to azabicycles 23-25 in excellent yields.

Intramolecular reactions of N-acyliminium intermediates 1, readily obtainable from succinimide, have proven to be eminently useful for the synthesis of azabicyclic compounds[1]. 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 2[2] and 3[3] are available from 1- and 4-substituted 1, respectively. Spiro system 4 arises, if R is located at position 5[4], and bridged system 5 is obtained, if R is at position 3[5]. In this communication we show that bridged system 6 is also easily accessible from succinimide by using N-acyliminium ion chemistry[6]. Azabicyclic 6 is the basic skeleton of pharmacologically important compounds like the tropane alkaloids[7] and anatoxin-a[8].

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



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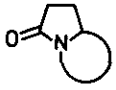

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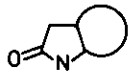

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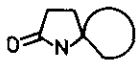

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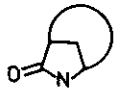

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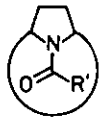

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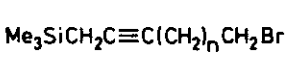
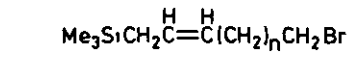
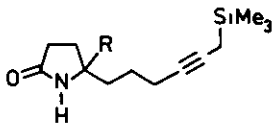


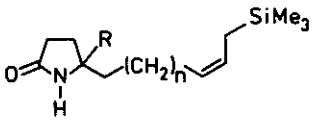
7 n = 1
8 n = 2



9 n = 1
10 n = 2



11 R = OH
14 R = H

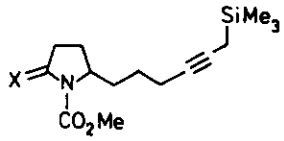


12 R = OH , n = 1
13 R = OH , n = 2
15 R = H , n = 1
16 R = H , n = 2

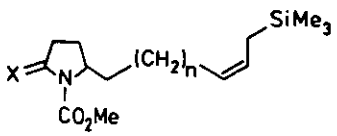
yields were obtained by using 3 eq of Grignard reagent[11]. Alternatively, one can first employ 1 eq of MeMgCl to make the succinimide salt, followed by 2 eq of the more expensive Grignard reagent. Bromide 7[9,10] was useless for our purposes, since all attempts to prepare its Grignard reagent failed. The crude hydroxy lactams 11-13 were not purified, but immediately reduced with $NaBH_3CN$ in acetic acid[12] to pyrrolidones 14-16[10]. 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 cyanoformate[13], furnishing 17-19[10] 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 $NaBH_4$ method[14] 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 23[10] in 70% overall yield from 17.

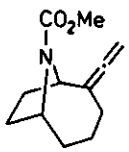


17 X = O
20 X = H,OH



18 X = O n = 1
19 X = O n = 2
21 X = H,OH n = 1
22 X = H,OH n = 2

The allenic structure was immediately apparent from the typical IR (1955 cm^{-1}) and ^{13}C NMR absorptions (δ204.5 and 204.1, 106.9 and 106.3, 75.0; most carbon atoms showed two peaks due to hindered rotation). Allylsilane 21 afforded olefin 24[10,15] as a single stereoisomer in 75% overall yield from 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 22 gave olefin 25[10,15] in addition to a small amount of its stereoisomer (ratio 19:1) in 73% overall yield from 19.



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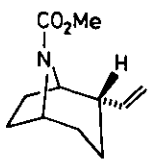

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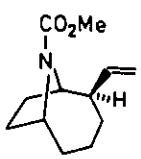

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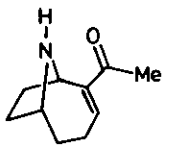
The cyclization product 23-25 were obtained in clean, fast and irreversible reactions. These reaction characteristics are on the one side a consequence of the favorable nucleophilic properties of allyl- and propargylsilanes, and on the other hand due to the high electrophilicity of N-acyliminium ions[16]. 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 (26) is a potent neurotoxin, produced by certain strains of the fresh water blue green alga Anabaena flos-aquae (Lyngb.) de Bréb[8]. This rather simple alkaloid with interesting pharmacological properties[17] has been synthesized both as racemate[18] and as pure enantiomer[17,19] by a number of research groups.

We herewith add a formal synthesis of racemic 26 starting from 25. Wacker oxidation[20] of the inseparable 19:1 mixture of 25 (CuCl (1 eq), $PdCl_2$ (0.2 eq), O_2, DMF,



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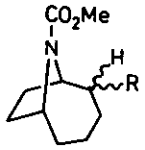
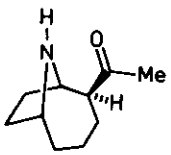


27 R = $COCH_3$
28 R = CH_2CHO



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H_2O) 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, Me_3SiCl) in refluxing acetonitrile[21] furnished (±)-dihydro-anatoxin-a as a 4:1 mixture[22] of 29 and its stereoisomer[23]. This completed a formal synthesis of racemic anatoxin-a, since Rapoport et al. have published[17] 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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10. New compounds gave correct high resolution mass data, and NMR and IR spectra in accord with their structure.

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22. The two steroisomers of 27 could be separated. Both of them gave the same 4:1 mixture on deprotection of nitrogen.

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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