

**SYNTHESIS OF 2,3-DIHYDRO-1H-PHENALENE DERIVATIVE BY THE
INTRAMOLECULAR DIELS-ALDER REACTION OF BENZYNE WITH FURAN**

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Summary: 2,3-Dihydro-1H-phenalene derivative **1** was synthesized by the intramolecular Diels-Alder reaction (**21**→**22**). 2,5-Dimethylpyrrole was used as a protecting group for the primary amine.

Interest in the 1H-phenalene ring system¹ originates from several directions. Early literature has been summarized by Reid² who includes references to the naturally occurring 1H-phenalene derivatives as plant and fungal pigments. Chemists have also been interested in this ring system as an organic ligand for the study of fluxionality and sigmatropic behavior associated with δ- and π-bonded metal derivatives of organic π ligands.^{3,4,5} Another related interest is in the 1,9-disubstituted-phenalenyl system. It possesses a frontier molecular orbital which fulfills the requirements of a model which provides a mechanism for the injection of π-electron spin density from a spiro substituent into a phosphazene linkage.⁶ Additional interest is in research aimed at the Favorski type zwitterion,⁷ and most recently in the pseudopterins, which are bioactive diterpene-pentose-glycosides.^{7a} We became interested in this ring system as a template which, when properly substituted as for example in **1**, bears a casual relationship to the morphine molecule.

Of direct preliminary synthetic interest for our template were four literature citations.⁸⁻¹¹ Bergson and Pikas⁸ used naphthalic anhydride (**2**) as the starting material for the carboxylic acid **3**. Violland *et al.* published two methods. In the first⁹ they used **3** to synthesize **4** and several N-substituted derivatives of **4**. In the second¹⁰ they used the amino acid **5** as a starting material for **6**. Evans and Waitt¹¹ employed the ketone of **7** to produce **8**. The synthetic methodology we encountered in this area can be summarized as cumbersome and may be further illustrated by the conversion of **9** to **10** which required eleven steps.¹²

In this communication, we describe the synthesis of 2-(di-n-propylamino)-2,3-dihydro-1H-phenalene-5-ol (**1**) employing as the key step the intramolecular Diels-Alder reaction¹³ of benzyne with furan. We were encouraged by the report of Best and Wege¹⁴ who described the synthesis of mansonone E, employing this principle. The required benzyne-furan intermediate was **11**. The precursor of **11** was **12**, which could be made from the reaction of **13** with **14**.

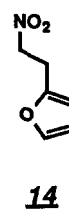
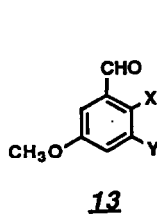
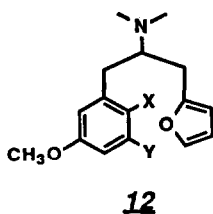
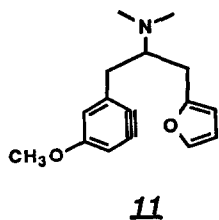
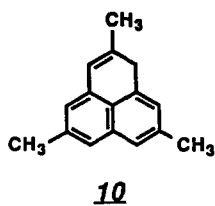
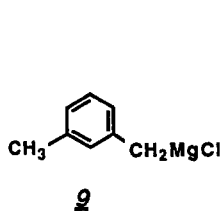
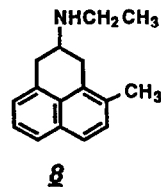
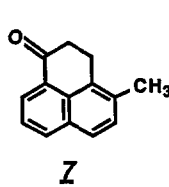
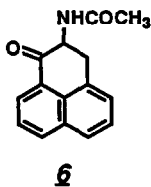
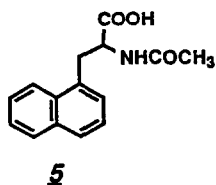
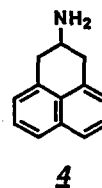
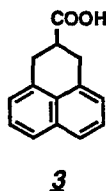
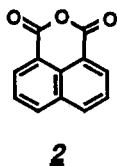
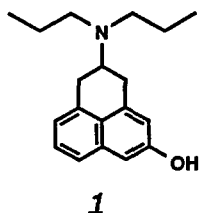
Two problems had to be overcome in designing the synthesis of **1** from aldehyde **13**. First, the choice had to be made as to the starting trisubstituted aldehyde **13** which would incorporate a compatible benzyne precursor. Second, the nitrogen functions had to be armed with a protecting group which would resist attack by phenyllithium, and which would also render the amine less nucleophilic in order to prevent its involvement with the benzyne moiety.¹⁵ It also had to be resistant to reductive conditions and acid hydrolysis.

As to the first problem, several workers have shown that o-dihaloarenes form benzyne when reacted with alkylolithium reagents.^{14,16} Recently, Gribble *et al.*¹⁷ have used 1-bromo-2-toluenesulfonyloxy substituted arenes in conjunction with phenyllithium to generate benzyne, and we chose to employ Gribble's strategy. As to the second problem, we eventually settled on the Breukelman *et al.* method,¹⁸ namely conversion of NH₂ to 2,5-dimethylpyrrole.

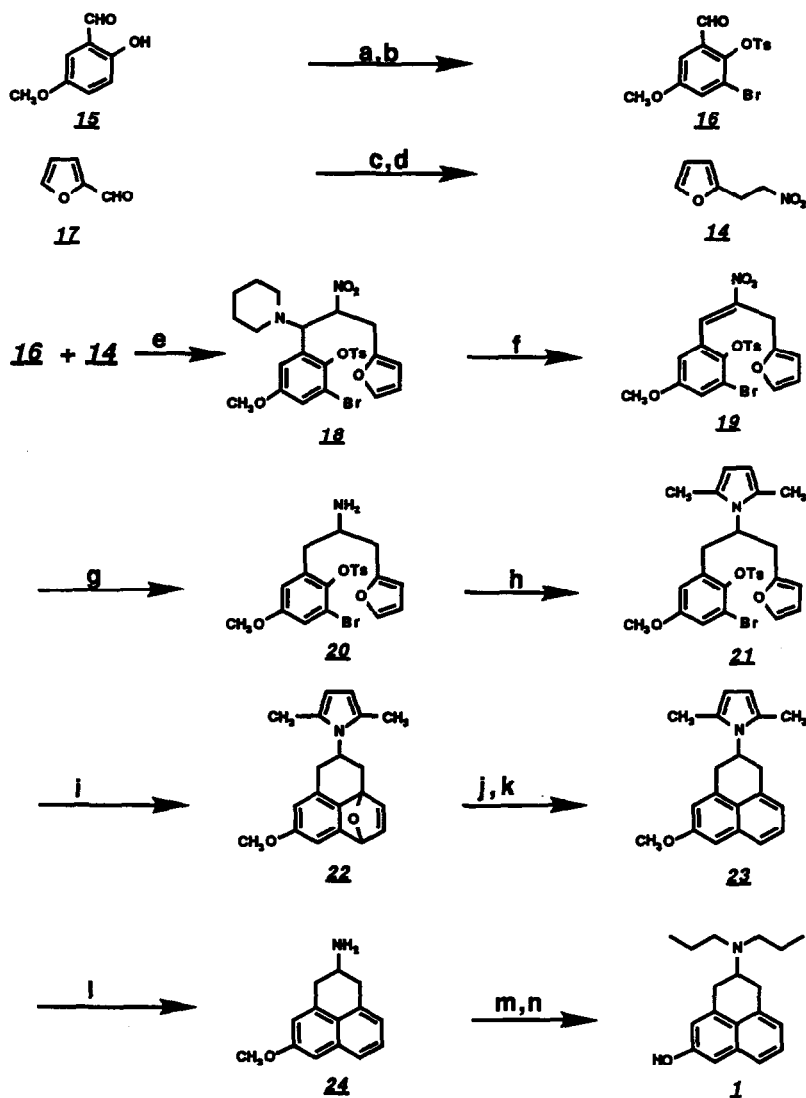
Our synthesis is shown in the Scheme.

2-Hydroxy-5-methoxybenzaldehyde (**15**) (purchased from Aldrich) was converted to the 3-bromo derivative^{19,20} and then tosylated to give the properly functionalized aldehyde **16**.²⁰ Knoevenagel reaction with aldehyde **16** and 2-(2-nitroethyl)furan (**14**, prepared in two steps from **17**) in Skellysolve B afforded the piperidine adduct **18**.²⁰ A full equivalent of the amine was used because the reaction was too slow when a catalytic amount of piperidine acetate was employed. The intermediate **18** was deaminated by stirring in a

slurry of silica gel in CH_2Cl_2 to give the unsaturated nitro compound 19.²⁰ Reduction of 19 with aluminum hydride²¹ gave the saturated amine 20.²⁰ Reaction with acetylacetone¹⁸ gave the 2,5-dimethylpyrrole derivative 21.²⁰ This benzyne precursor was treated with phenyllithium in THF at 10° to give the Diels-Alder product 22.²⁰ The olefin 22 was reduced with either Mg in MeOH²² or by hydrogenation in THF, in both methods using 10% Pd-C as the catalyst, to give the saturated compound.²⁰ The oxo bridge was opened with HCl-ether, or preferably with $\text{BF}_3\text{-CH}_2\text{Cl}_2$ to give the 2,3-dihydro-1H-phenalene product 23.²⁰ The 2,5-dimethylpyrrole protecting group was removed¹⁸ by refluxing with hydroxylamine hydrochloride and sodium bicarbonate in EtOH to give the primary amine 24.²⁰ This amine was alkylated with n-propyl bromide and potassium carbonate in acetonitrile to give N,N-dipropylamine derivative.²⁰ Finally, the methyl ether was cleaved with 48% aqueous hydrobromic acid to give the target phenol 1, isolated as the hydrobromide.²⁰

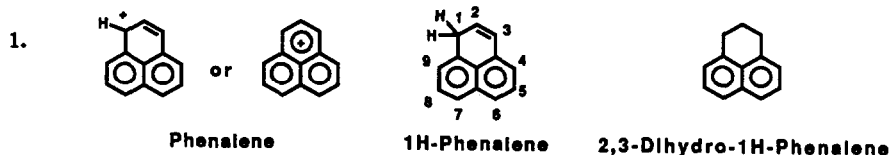


Scheme



a. Br_2 , NaOAc, AcOH, 81%; b. TsCl, NaOH, THF, quant; c. CH_3NO_2 , β -Alanine, Ethanol, 47%;
 d. NaBH_4 , Isopropanol, THF, 80%; e. Piperidine, AcOH, Skellysolve B; f. SiO_2 , CH_2Cl_2 , 65%;
 g. AlH_3 , THF, quant; h. 2,5-Pentanedione, Propionic Acid, Benzene, 70-80%; i. Phenyllithium,
 THF, 10°C, 2 hr.; j. Mg, CH_3OH , 10% Pd/C or H_2 , 10% Pd/C, THF, 74% from **22**; k. HCl,
 Ether or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 75%; l. $\text{NH}_2\text{OH} \cdot \text{HCl}$ (12 mole equiv), NaHCO_3 (8 mole equiv), Ethanol,
 reflux, 79%; m. n-propyl bromide, K_2CO_3 , CH_3CN , reflux, 66%; n. 48% HBr, 120°C, 63%.

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