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by

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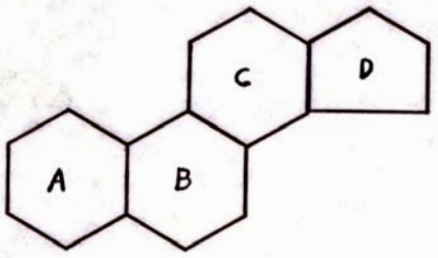
Natural products chemistry is a very important field of chemistry to chemists, biochemists, and biologists. The ability to synthesize a naturally occurring chemical in the laboratory is necessary for some experiments. Often it is difficult to isolate a large quantity of a compound from its natural source when needed for certain experiments. Established procedures for artificial synthesis of this compound can produce higher yields. Sometimes, the function of a natural product is tested by observing the behavior of analogues in the same biological system. The differences in behavior can be related to differences in structure. Since such analogues are not produced naturally, they have to be synthesized in the lab. The goals of natural products chemistry are to increase available quantity and to provide possible methods for variation.

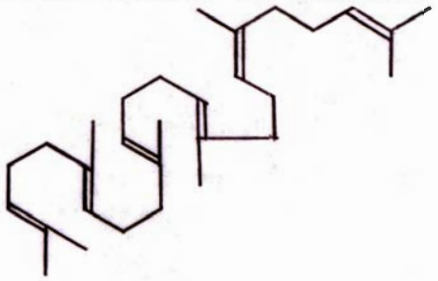
One major classification of compounds that are found in biological systems is the terpenoids. These compounds all have structures which are derived from the assembly of isoprene building blocks. In biological systems, isoprene is usually found in the form of isopentenyl pyrophosphate. Derivatives of isoprene oligomers are very common in nature, and some of them are familiar in their commercial use, such as camphor, α-phellandrene (eucalyptus), menthol, menthone, citral and limonene (lemon oil), cembrene (pine oil), pinene (turpentine), vitamin A, ß-carotene, and squalene (shark liver oil). The all *cis* polymer of isoprene is the major constituent of natural rubber.

A subclass of the terpenoids is a group of compounds which all are based on the structure of perhydrocyclopentanophenanthrene (I). They include sterols, steroids, bile acids, some other hormones, and many pharmaceuticals. Some of the more familiar compounds include cholesterol, vitamin D_3, cholic acid, cortisone, progesterone, testosterone, and estradiol.

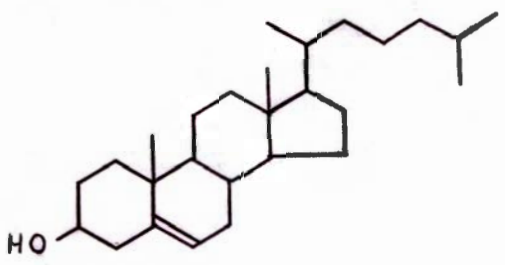


(I)

These compounds all are based on the same tetracyclic ring structure, but their synthesis is not derived from perhydrocyclopentanophenanthrene. A complicated pathway is involved. In biochemical systems, this usually involves the isoprene building blocks. A typical example of this is the synthesis of cholesterol (II) from squalene (III). In the laboratory, even more creativity is required, as some biochemical reactions cannot be mimicked.

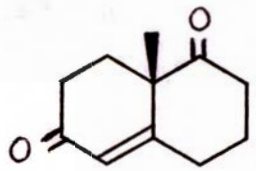


(III)



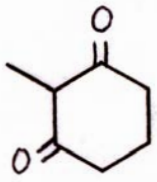
(II)

For several decades, 3,4,8,8a-tetrahydro-8a-methyl-1,6(*2H,7H*)-naphthalenedione (Wieland-Miescher ketone) **(IV)** has been recognized as an important compound in the field of natural products chemistry. The compound, which itself is a natural product, was first isolated by Wieland and Miescher[1] in 1950 from several organisms. Soon afterward, studies showed its biological activity[2,3,4] and its importance as an intermediate in the synthesis of natural products as described above.[5,6,7] Wieland-Miescher ketone is often the source of the carbon skeleton for the A and B rings of these tetracyclic compounds.



(IV)

The most common procedure for the synthesis of Wieland-Miescher ketone usually involves two reactions. The first reaction is a Michael addition of 2-methyl-1,3-cyclohexanedione (2-methyldihydroresorcinol) **(V)** to 3-buten-2-one (methyl vinyl ketone) **(VI)**. The second reaction is a Robinson annulation to form Wieland-Miescher ketone.

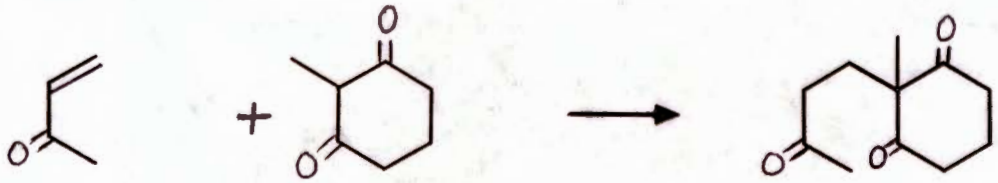


(V)

(VI)

A Michael addition is a conjugate addition to an α,ß-unsaturated carbonyl compound using an enolate ion as a

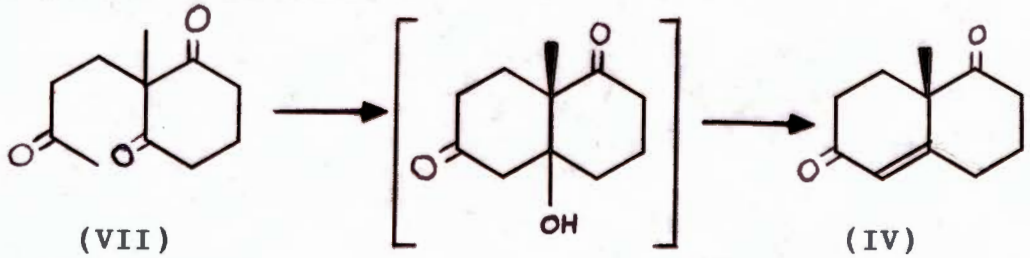
nucleophile. The reaction takes place in a variety of solvents, but requires the presence of a base as a catalyst. In this case, methyl vinyl ketone is the α,ß-unsaturated compound, and 2-methyldihydroresorcinol is the enolate nucleophile. This reaction forms the trione 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (VII) (see equation 1).



(1)

(VI) (V) (VII)

A Robinson annulation is an intramolecular aldol condensation used to build a ring onto some starting molecule. The reaction is really an intramolecular aldol addition followed by the removal of water, but the intermediate is rarely isolated. This reaction also requires a base to be present as a catalyst. In this case, the trione undergoes the Robinson annulation to form Wieland-Miescher ketone (see equation 2).



(2)

(VII) (IV)

Since the discovery of Wieland-Miescher ketone and its significance, several methods have been developed to synthesize it in the lab. The first important procedure was developed by Newman and his associates[5,6,8] in 1958. In this reaction, methyl vinyl ketone (or a dialkylamino derivative) and 2-

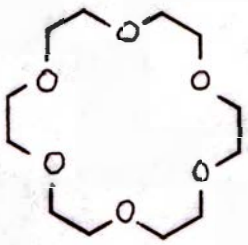
methyldihydroresorcinol react in the presence of a base such as pyridine, pyrrolidine, or triethylamine with benzene as the solvent. A Dean-Stark phase-separating head was used to remove the water as is evolved from the condensation step.

The second important procedure was developed and patented in 1971 by Z. G. Hajos and D. R. Parrish of Hoffman-La Roche Company. This reaction requires an optically pure base, usually proline, in an aprotic polar solvent for the Robinson annulation step. This method exploits the fact that using an optically pure catalyst will produce an optically pure sample of Wieland-Miescher ketone.

Other variations on this two-step synthesis have been developed, including using potassium hydroxide as the base and methanol as the solvent in the first step,[6] using heat as the only catalyst of the whole reaction,[9] and using acetic acid as the catalyst and water as the solvent for the first step.[10] All of the methods published in the literature report an overall yield of 56.8 percent to 80 percent for this reaction. The yield is lowered by imperfect reaction conditions, the need to change solvents between steps, and purification techniques required to obtain optically pure samples.

In related research, Belsky[11] reported that the Michael addition reaction can be catalyzed in aprotic solvents using potassium fluoride (KF) in the presence of 1,4,7,10,13,16-hexaoxacycloöctadecane (18-crown-6) **(VIII)**. The 18-crown-6 forms a complex with the potassium ion, producing a "naked" fluoride

ion which is reported to be an efficient and powerful base catalyst for Michael additions. The literature reports yields of up to 94 percent.



(VIII)

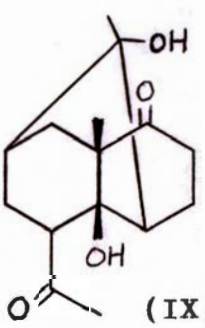
The goal of this research is to apply the naked fluoride procedure to the synthesis of Wieland-Miescher ketone to increase the overall yield. Applying this procedure to the synthesis of Wieland-Miescher ketone provides two unique situations.

First, the enolates that were used by Belsky all involved methylene carbon atoms, but in this reaction, the 2-methyldihydroresorcinol carbon atom is a *methyne* carbon. This makes the system somewhat unique. If the Michael addition is successful in good yields, a research topic could branch from this, involving a systematic study of naked fluoride-catalyzed Michael additions of the methyne carbon of 2-methyldihydroresorcinol to various other α,ß-unsaturated carbonyl compounds.

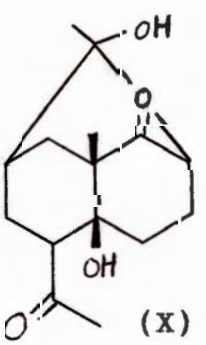
Second, the naked fluoride-catalyzed reaction takes place in an aprotic, nonpolar solvent, which has not always been the case in previous work. Therefore, the solvent does not have to be removed between the two steps. The second base catalyst, such as proline, can be added right to the reaction mixture, making it a

one-pot synthesis. Also, if the fluoride works as well as reported by Belsky, it may be a strong enough base to catalyze the second step itself in high yield, although the optical purity would not be present.

Our research shows that the fluoride ion is very effective in catalyzing the Michael addition of 2-methyldihydroresorcinol to methyl vinyl ketone. When an excess of methyl vinyl ketone is used, 2-methyldihydroresorcinol adds to methyl vinyl ketone, forming the trione. This, in turn, becomes the enolate and adds to another methyl vinyl ketone. The resulting compound then undergoes two intramolecular aldol additions to form a tricyclic compound, either 8-acetyl-8a,9-dihydroxy-4a,9-dimethyl-2,3,5,7-tetrahydro-1,6-methanonaphthalen-4-one (IX) or 5-acetyl-4a,9-dihydroxy-8a,9-dimethyl-3,4,6,8-tetrahydro-2,7-methanonaphthalen-1-one (X). Both of these compounds are unreported in the literature.



(IX)



(X)

When equimolar amounts of 2-methyldihydroresorcinol and methyl vinyl ketone are used, the trione is produced in 75 percent yield. Despite this success, it is not yet possible to continue the reaction to form Wieland-Miescher ketone. Several measures have been taken to move the condensation along, but

water-free reagents, molecular sieves, and toluene as the solvent (which refluxes at a higher temperature) have had little effect.

The reaction was also performed using 2-propenal (acrolein) as the α,ß-unsaturated carbonyl compound, but the Michael addition was not very successful. The anticipated compound was on of several products in the low-yield mixture.

Subsequent reactions will involve the use of a phase-separating head to remove the water from the reaction and/or proline added to the reaction to catalyze the second step.

Experimental.

Purification of 2-methyldihydroresorcinol **(V)** Crude **(V)**[12] was dissolved in hot 95% EtOH until the solution was nearly saturated. The solution was filtered hot, cooled and recrystallized. The crystals were collected by vacuum filtration, rinsed with diethyl ether, and dried. A second crop of crystals was obtained by letting the filtrate stand for several days at room temperature. The melting point of the light pink crystals was 207-209°C (sealed tube). ^{1}HNMR: δ(d_6-DMSO) 1.54(s), 2.30(t), 2.5(m) and 10.3(broad s).

Tricyclic compound **(IX)** or **(X)**. In a 250-ml round-bottomed flask equipped with stir bar was placed 1.26g (10mmol) of **(V)**, 8ml (100mmol) distilled methyl vinyl ketone **(VI)**, 5.8g (100mmol) KF, 0.52g (3mmol) 18-crown-6 **(VIII)**, and 4g molecular sieves in 100ml benzene. The mixture was refluxed with stirring for 5 hours.

The mixture was cooled to room temperature and then filtered to remove the KF and sieves. The solvent was removed by vacuum distillation. The remaining mixture was dissolved in CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. The solvent was again removed. The resulting oil yielded crystals after standing at room temperature for several days. The crystals were rinsed with CCl_4. The melting point was 178-180°C. ^{1}HNMR: $\delta(CDCl_3)$ 1.13(s), 1.17(s), 2.35(s), 2.53(s), 3.23(dd), and 5.71(s). ^{13}CNMR: $\delta(CDCl_3)$ 18.66, 24.69, 24.94, 28.31, 28.69, 31.89, 33.87, 41.40, 42.34, 48.91, 51.85, 76.09, 76.39, 213.5, 219.5. IR: 1711cm^{-1}.

2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (VII). In a 250-ml round-bottomed flask equipped with stir bar was placed 1.78g (14.1mmol) of (V), 5.8g (100mmol) KF, and 0.52g (3mmol) of (VIII) in 50ml benzene. The mixture was refluxed for 10 minutes. To the mixture was added 0.99g (14.1mmol) of distilled (VI) and 30ml benzene. The reaction mixture was refluxed with stirring for 6 hours. The mixture was cooled to room temperature and then filtered to remove the KF. The solvent was removed by vacuum distillation. The remaining mixture was dissolved in ethyl acetate, washed with H_2O, washed with sat. NaCl(aq), and dried over $MgSO_4$. The solvent was removed and CCl_4 was added and removed. The resulting oil yielded 74.8%.

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