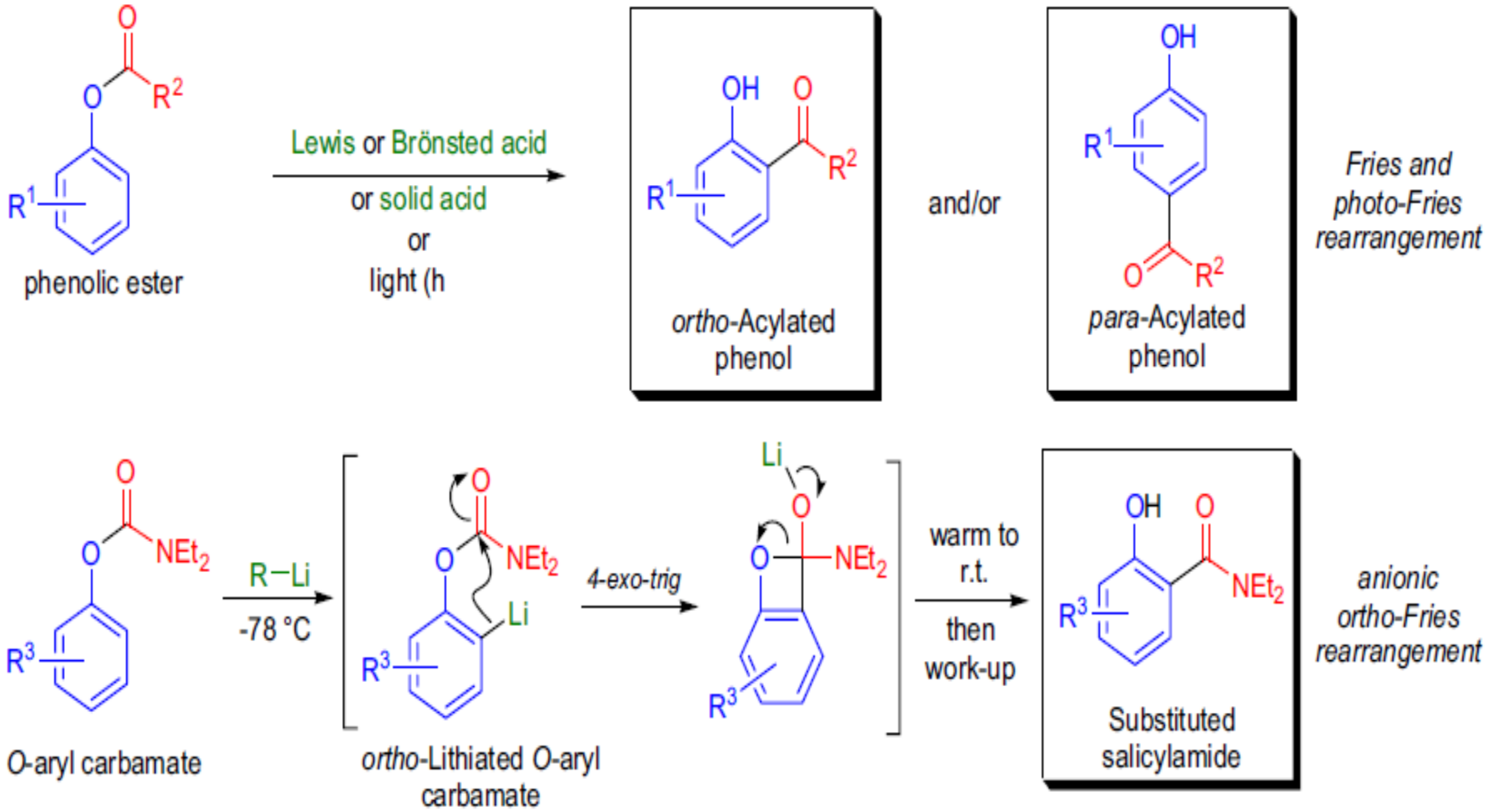
FRIES-, PHOTO-FRIES, AND ANIONIC ORTHO-FRIES REARRANGEMENT

(References are on page 590)

Importance:

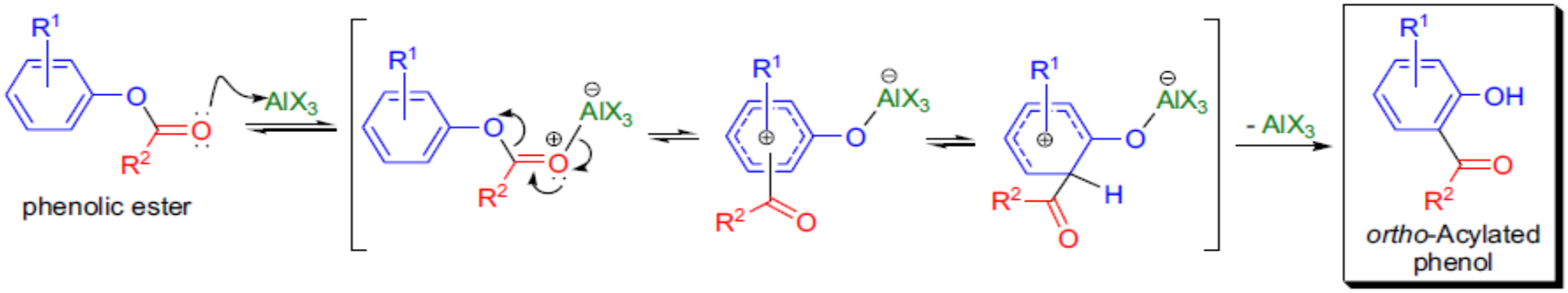
[*Seminal Publications*[1-4]; *Reviews*[5-14]; *Modifications & Improvements*[15-31]; *Theoretical Studies*[32-38]]

In the early 1900s, K. Fries and co-workers reacted phenolic esters of acetic and chloroacetic acid with aluminum chloride and isolated a mixture of *ortho*- and *para*-acetyl- and chloroacetyl phenols.[3,4] Reports in the literature described similar rearrangements in the presence of Lewis acids during the late 1800s,[1,2] but Fries was the one who recognized that the rearrangement of phenolic esters was general. In his honor the conversion of phenolic esters to the corresponding *ortho* and/or *para* substituted phenolic ketones and aldehydes, in the presence of Lewis or Brönsted acids is called the *Fries rearrangement*. The *Fries rearrangement* has the following general features: 1) usually it is carried out by heating the phenolic ester to high temperatures (80-180 °C) in the presence of at least one equivalent of Lewis acid or Brönsted acid (e.g., HF, $HClO_4$, PPA); 2) the reaction time can vary between a few minutes and several hours; 3) Lewis acids that catalyze the *Friedel-Crafts acylation* are all active but recently solid acid catalysts (e.g., zeolites, mesoporous molecular sieves) and metal triflates have also been used;[12,30] 4) the rearrangement is general for a wide range of structural variation in both the acid and phenol component of phenolic esters; 5) yields are the highest when there are electron-donating substituents on the phenol, while electron-withdrawing substituents result in very low yields or no reaction; 6) with polyalkylated phenols alkyl migration is often observed under the reaction conditions; 7) the *Friedel-Crafts acylation* of phenols is usually a two-step process: formation of a phenolic ester followed by a *Fries rearrangement*; 8) the selectivity of the rearrangement to give *ortho*- or *para*- substituted products largely depends on the reaction conditions (temperature, type, and amount of catalyst, solvent polarity, etc.); 9) at high temperatures without any solvent the *ortho*-acylated product dominates while low temperatures favor the formation of the *para*-acylated product; 10) with increasing solvent polarity the ratio of the *para*-acylated product increases; and 11) optically active phenolic esters rearrange to optically active phenolic ketones. There are two main variants of the *Fries rearrangement*: 1) upon irradiation with light phenolic esters undergo the same transformation, which is known as the *photo-Fries rearrangement*;[8,11] and 2) an *anionic ortho-Fries rearrangement* takes place when *ortho*-lithiated *O*-aryl carbamates undergo a facile *intramolecular [1,3]-acyl migration* to give substituted salicylamides at room temperature.[17,27]


phenolic ester
Lewis or Brönsted acid
or solid acid
or
light (h
ortho-Acylated phenol
and/or
para-Acylated phenol
Fries and photo-Fries rearrangement
O-aryl carbamate
R−Li
-78 °C
ortho-Lithiated O-aryl carbamate
4-exo-trig
warm to r.t.
then work-up
Substituted salicylamide
anionic ortho-Fries rearrangement
R1 = alkyl, -OR,-NR2, -aryl; R2 = alkyl, aryl; R3 = alkyl, -OR, Cl

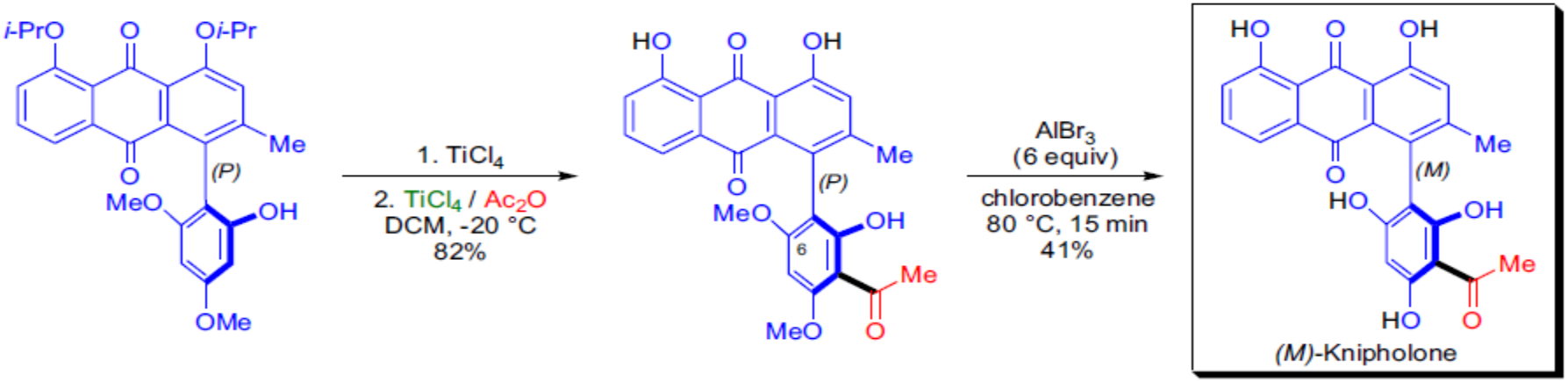
Mechanism: [39-49,11,50]

The *Fries rearrangement* proceeds *via* ionic intermediates but the exact mechanistic pathway (whether it is inter- or intramolecular) is still under debate. There are many reports in the literature that present evidence to support either of the pathways, but it appears that the exact route depends on the structure of the substrates and the reaction conditions. The scheme depicts the formation of an *ortho*-acylated phenol from a substituted phenolic ester in the presence of aluminum trihalide catalyst. The *photo-Fries rearrangement* proceeds *via* radical intermediates.[11,50,13]

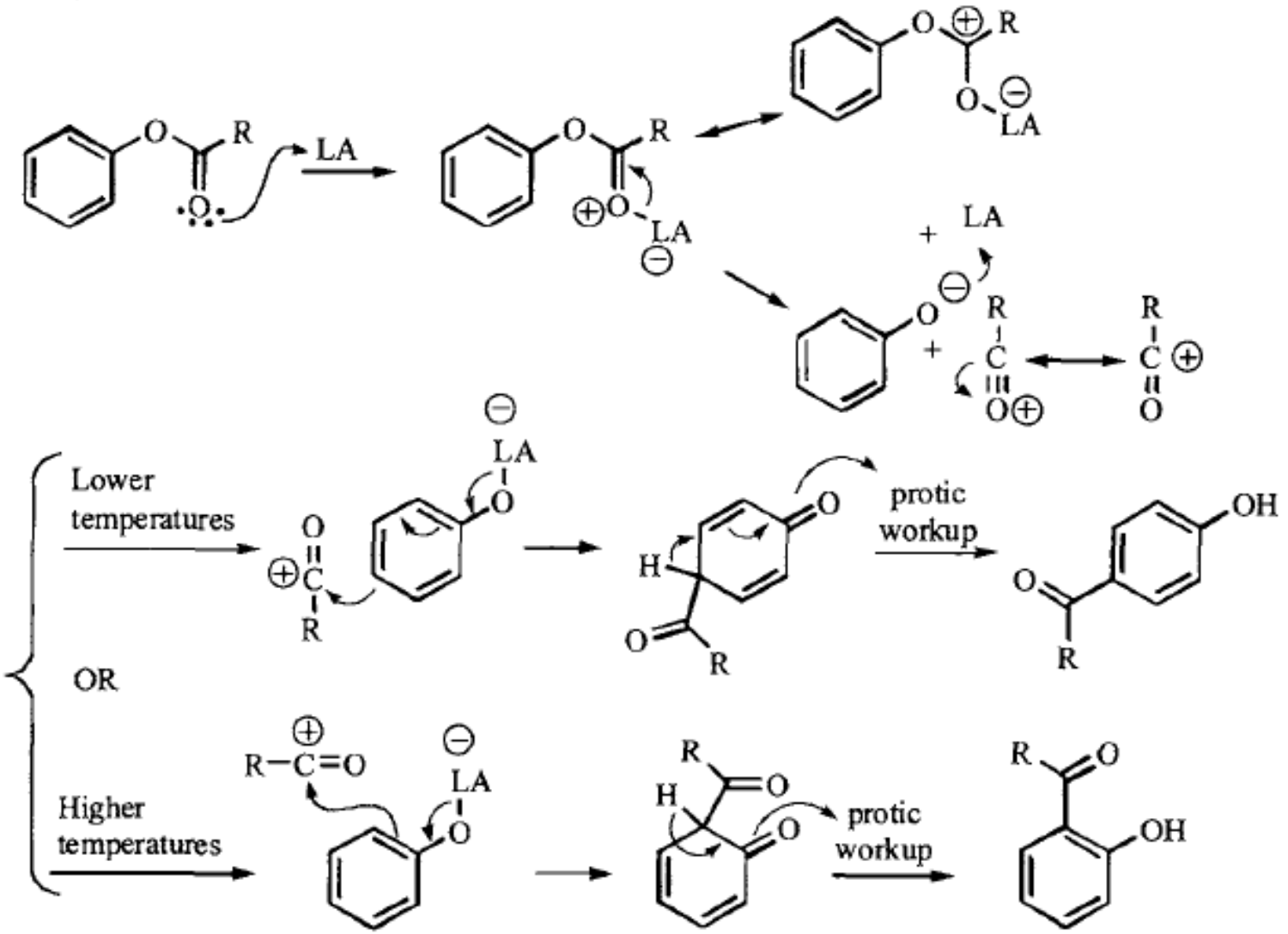


Synthetic Applications:

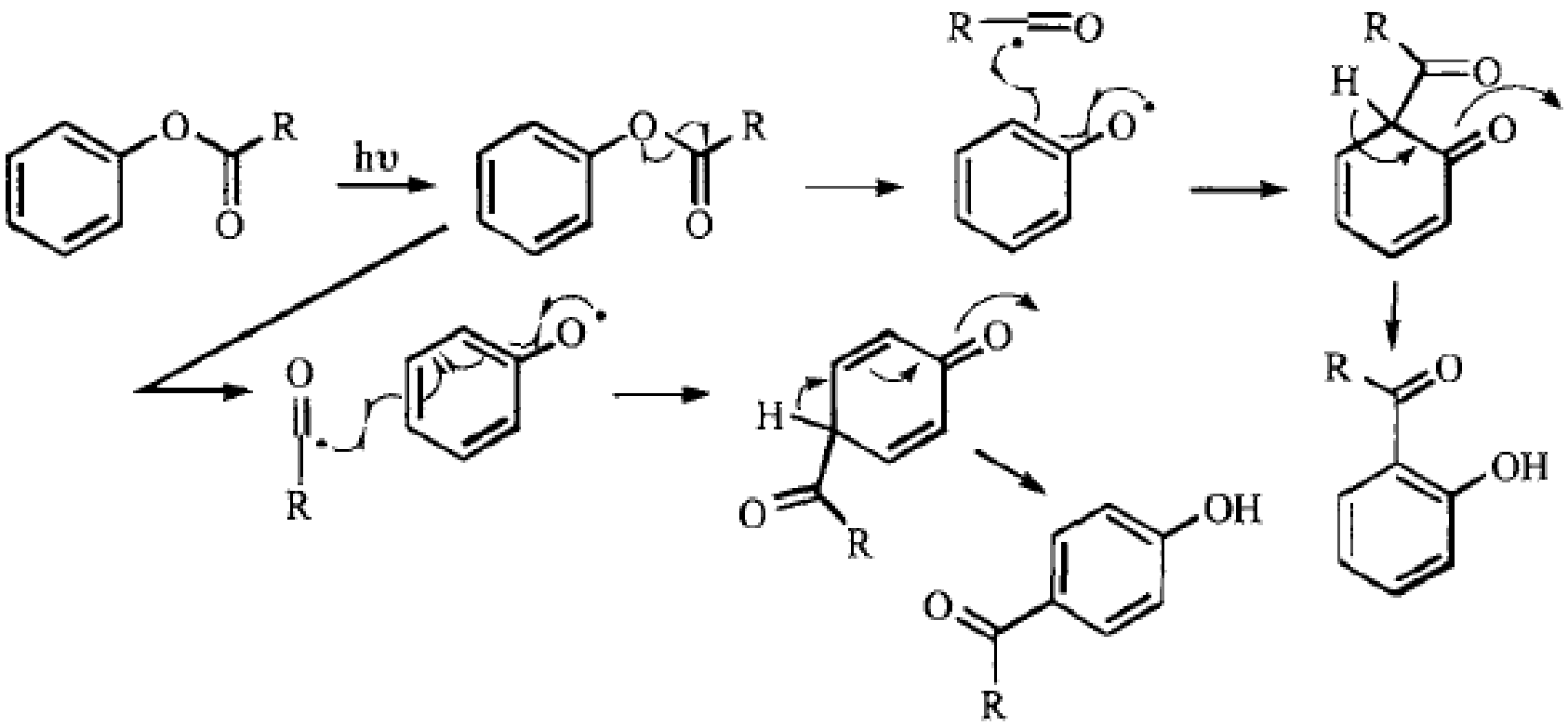
The first atropo-enantioselective total synthesis of a phenylanthraquinone natural product (*M*)-knipholone was reported by G. Bringmann et al.[51] In the late stages of the synthesis, an acetyl group had to be introduced under mild conditions. The advanced substituted anthraquinone intermediate was first deprotected with $TiCl_4$ and then acylated with Ac_2O in the presence of $TiCl_4$. A spontaneous *Fries-rearrangement* took place to afford the *ortho*-acylated product in high yield. The natural product was obtained by a mono *O*-demethylation at C6 with $AlBr_3$.



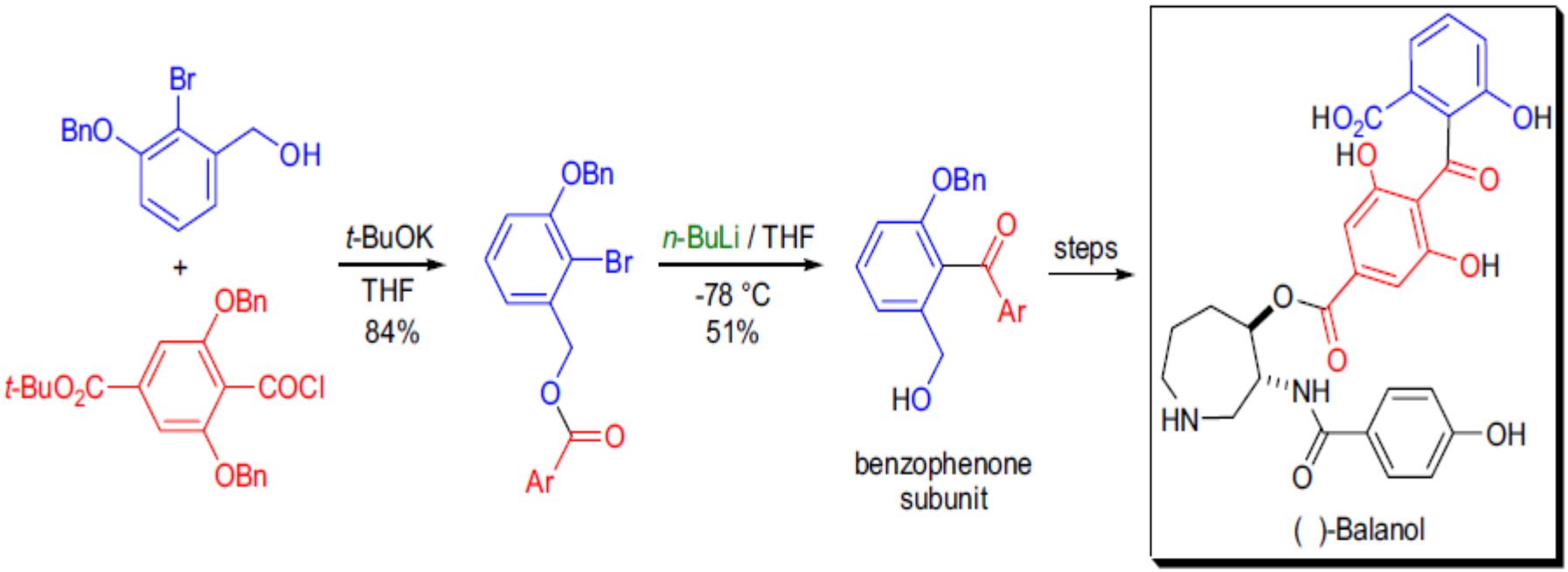
Proposed Mechanism:



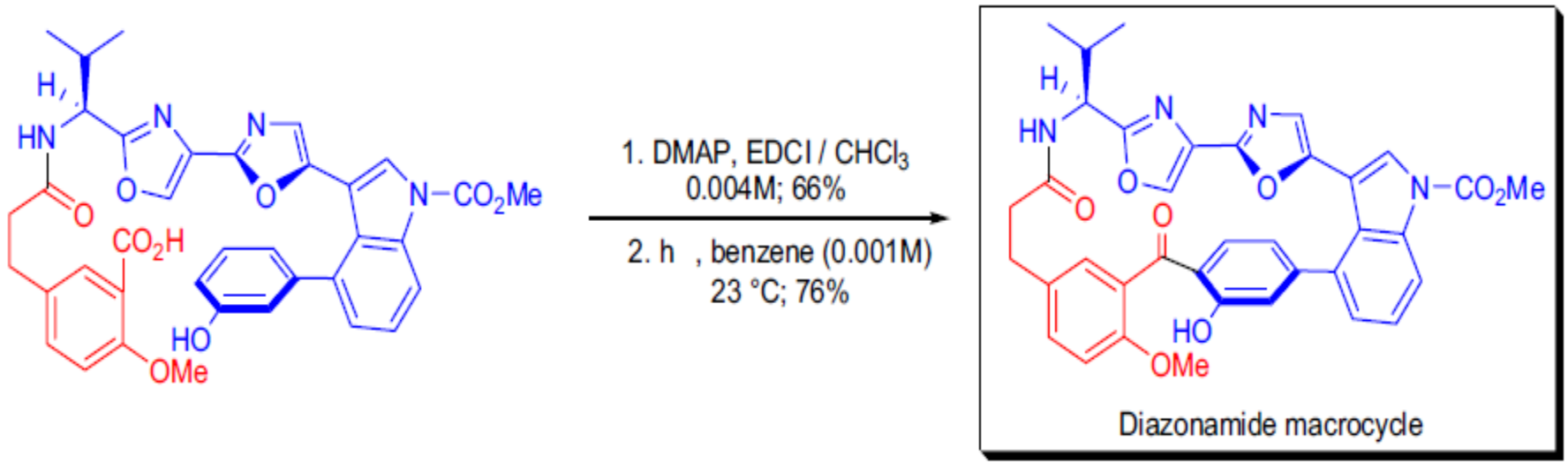
***The Photo-Fries Reaction*:**



The total synthesis of the potent protein kinase C inhibitor (–)-balanol was accomplished by J.W. Lampe and co-workers.[52] They took advantage of the *anionic homo-Fries rearrangement* to prepare the sterically congested benzophenone subunit. To this end, 2-bromo-3-benzyloxy benzyl alcohol was first acylated with a 1,3,5-trisubstituted benzoyl chloride to obtain the ester precursor in 84% yield. Next, the ester was treated with *n*-BuLi at -78 °C to perform a metal-halogen exchange. The resulting aryllithium rapidly underwent the *anionic homo-Fries rearrangement* to afford the desired tetra *ortho*-substituted benzophenone in 51% yield.



Research in the laboratory of P. Magnus showed that the macrocyclic skeleton of diazonamide could be synthesized with the use of *macrolactonization* followed by a *photo-Fries rearrangement*.[53] First, the aromatic carboxylic acid and the phenol were coupled with EDCI to form the macrolactone (phenolic ester), which was then exposed to light at high-dilution to cleanly afford the macrocyclic *ortho*-acylated phenol skeleton of diazonamide.

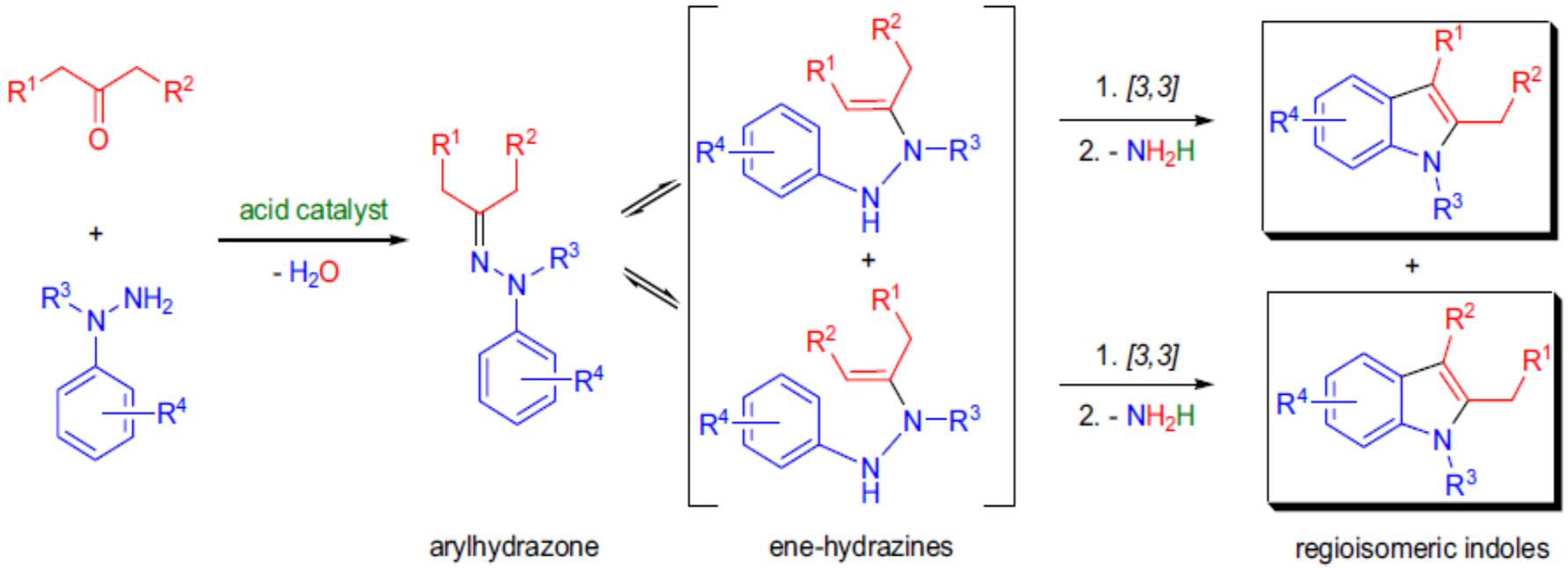


FISCHER INDOLE SYNTHESIS

Importance:

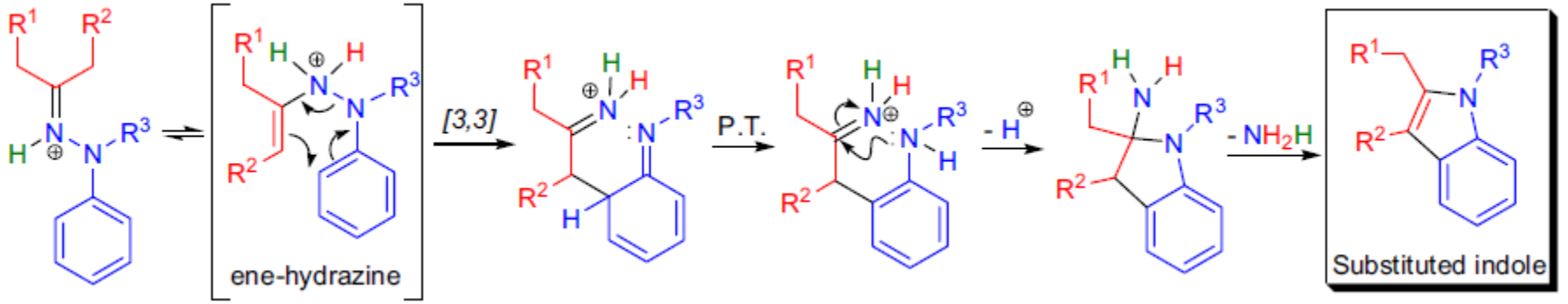
[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-13]; *Theoretical Studies*[14-21]]

In 1883, E. Fischer and F. Jourdan[1] treated pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride, and the product of this reaction was later identified as 1-methylindole-2-carboxylic acid.[2] The preparation of indoles by heating arylhydrazones of ketones or aldehydes in the presence of a protic acid or a Lewis acid catalyst is known as the *Fischer indole synthesis*. Since its discovery, it has become the most important method to prepare substituted indoles. The catalysts that successfully lead to indolization are: 1) strong acids (e.g., PTSA, PPA, HCl, H_2SO_4); 2) weak acids (e.g., pyridinium chloride, AcOH); 3) solid acids (e.g., montmorillonite KSF clay, Mordenite, Zelotite Y, ion-exchange resins); and 4) Lewis acids (PCl_3, polyphosphoric acid trimethylsilyl ester, $ZnCl_2$). The Lewis acid catalyzed reactions often proceed under milder conditions (room temperature rather than high temperature) than the reactions catalyzed by protic acids. In the case of heteroaromatic arylhydrazones, however, the use of any acid is problematic (due to the protonation of the heteroatom), and for these compounds simple heating at high temperatures (thermal non-catalytic method) can also lead to indolization. The acid catalyzed cyclizations are usually 7 to 30 times faster than the thermal reactions. The main features of the *Fischer indole synthesis* are the following: 1) it is not necessary to isolate the arylhydrazones, the indole formation can be conducted by mixing the aldehyde and hydrazine and carrying out the indolization in one-pot; 2) unsymmetrical ketones give two regioisomeric 2,3-disubstituted indoles, and the regioselectivity depends on a combination of factors: acidity of the medium, substitution of the hydrazine, steric effects in the ketone and in the ene-hydrazines; 3) with unsymmetrical ketones indolization usually occurs at the least substituted α-carbon atom in strongly acidic medium, whereas weak acids give rise to the other regioisomer; 4) indolization of α,β-unsaturated ketones is generally unsuccessful due to the formation of unreactive pyrazolines; 5) 1,2-diketones can give both mono- and *bis*-indoles and the mono-indoles are usually formed with strong acid catalysts in refluxing alcohols; 6) 1,3-diketones and β-keto esters are not ideal substrates, since their arylhydrazones form pyrazoles and pyrazol-3-ones, respectively; 7) due to their sensitivity, aldehydes are used in their protected forms (acetal, aminal, or bisulfite addition product), and they give rise to 3-substituted indoles; 8) hydrazines are often used as their HCl salt or in their Boc protected form (they are not very stable in their free base form); 9) electron-withdrawing substituents on the aromatic ring of the hydrazine causes the indolization to become low-yielding and slow; 10) *ortho*-substituted arylhydrazines generally react much slower than the *meta*-substituted ones; and 11) the *Japp-Klingemann reaction* provides an easy way to obtain the starting arylhydrazones from β-dicarbonyls and arenediazonium salts.



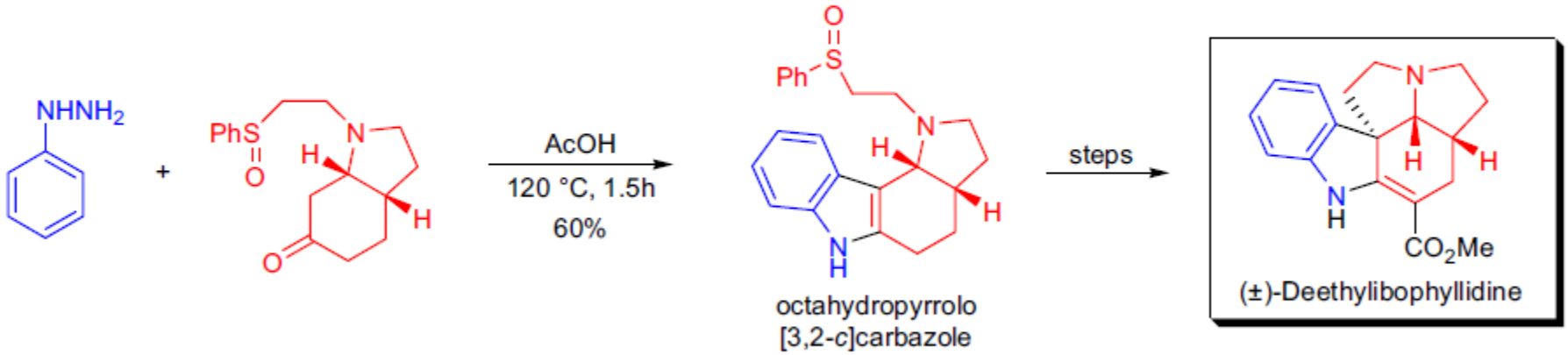
Mechanism: [22-39]

The currently accepted mechanism of the *Fischer indole synthesis* was originally proposed by R. Robinson in 1924.[22] There are five distinct steps: 1) coordination of the Lewis acid (e.g., proton) to the imine nitrogen; 2) tautomerization of the hydrazone to the corresponding ene-hydrazine; 3) disruption of the aromatic ring by a *[3,3]-sigmatropic rearrangement*; 4) rearomatization *via* a proton shift and formation of the 5-membered ring by a favored *5-exo-trig* cyclization; and 5) the loss of a molecule of ammonia to finally give rise to the indole system.



Synthetic Applications:

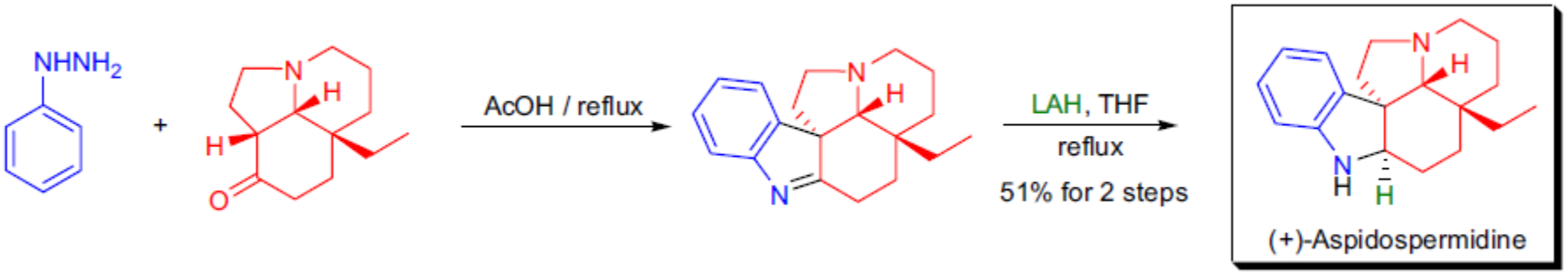
The total synthesis of (±)-deethylibophyllidine was accomplished by J. Bonjoch and co-workers, who applied a regioselective *Fischer indole synthesis* as one of the key steps to obtain octahydropyrrolo[3,2-*c*]carbazoles.[40] The indole formation was followed by a tandem *Pummerer rearrangement-thionium ion cyclization* to generate the quaternary spiro stereocenter.



octahydropyrrolo
[3,2-*c*]carbazole

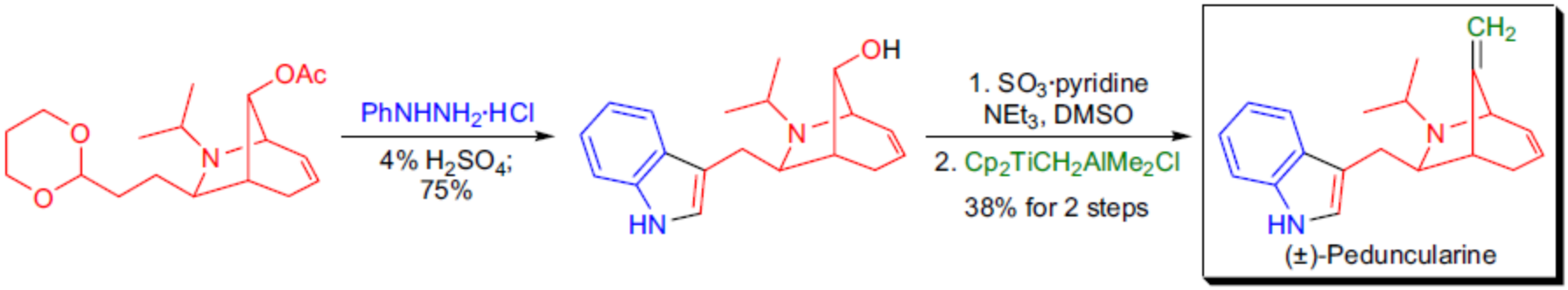
(±)-Deethylibophyllidine

During the total synthesis of (+)-aspidospermidine by J. Aubé et al., the final steps involved an efficient *Fischer indolization* of a complex tricyclic ketone.[41] This ketone was unsymmetrical and the indole formation occurred regioselectively at the most substituted α-carbon in a weakly acidic medium (glacial AcOH).



(+)-Aspidospermidine

The unusual 6-azabicyclo[3.2.1]oct-3-ene core of the alkaloid (±)-peduncularine was assembled using the [3+2] annulation of an allylic silane with chlorosulfonyl isocyanate by K.A. Woerpel and co-workers.[42] In the endgame of the total synthesis, the bicyclic aldehyde was masked as the acetal, and an efficient *Fischer indole synthesis* was performed using phenylhydrazine hydrochloride along with 4% H_2SO_4. Several subsequent steps led to the natural product.



J.M. Cook et al. accomplished the enantiospecific total synthesis of the indole alkaloid tryprostatin A.[43] The substituted indole nucleus was assembled at the beginning of the synthesis, and the necessary arylhydrazone was prepared *via* the *Japp-Klingemann reaction* using the diazonium salt derived from *m*-anisidine and the anion of ethyl-α-ethylacetoacetate. The regioselectivity of the *Fischer indole synthesis* favored the 6-methoxy-3-methylindole-2-carboxylate regioisomer in a 10:1 ratio.