Synthesis of the Cardiotonic Bemarinone, 5,6-Dimethoxy-4-methyl-2(1*H*)-quinazolinone, Utilizing a Directed Metalation Approach

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Received January 3, 1995

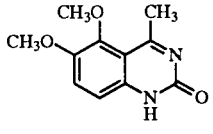
Dedicated to Professor Stuart S. Kulp on his retirement from the Department of Chemistry, Moravian College, Bethlehem, Pennsylvania.

Several methods for the synthesis of bemarinone, 5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone, were explored with the most successful being a directed metalation route. Details of the lithiation and the subsequent reaction with electrophiles of 3',4'-dimethoxy-2,2-dimethylpropioanilide and other derivatives of 3,4-dimethoxyaniline are given.

J. Heterocyclic Chem., **32**, 761 (1995).

Introduction.

The search for a replacement for digitalis in the treatment of congestive heart failure is proceeding rapidly within the drug industry [1]. Work in our medicinal chemistry laboratories led to 5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone (**1**, RWJ 16600, bemarinone), a potent inhibitor of cardiac fraction III cyclic nucleotide phosphodiesterase with potential as a positive inotrope [2a,b].



1, RWJ 16600

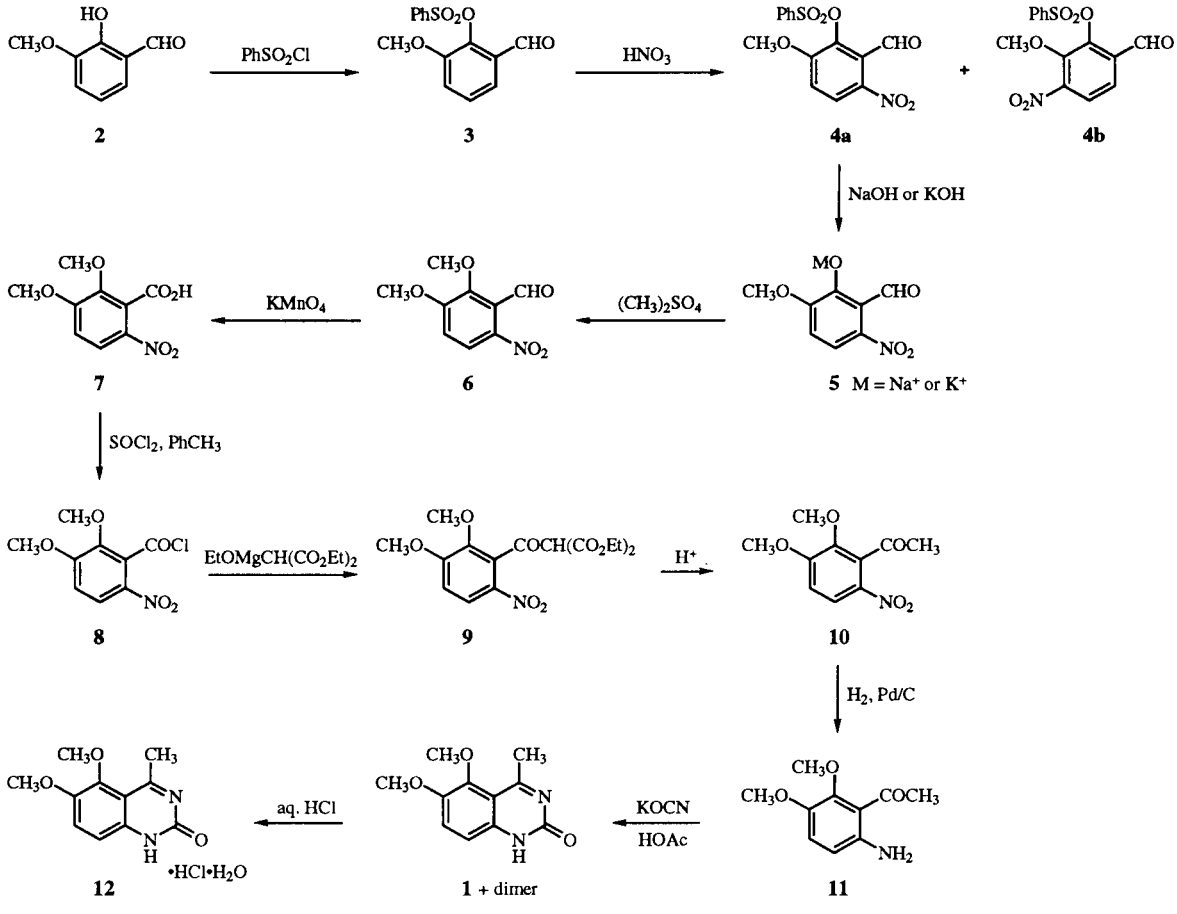
The original method for the preparation of **1** is shown in Scheme I [2c,d] and was used to prepare material for initial pharmacological screening.

When the project reached the chemical development laboratories, our first task was the critical evaluation of the original synthetic route. Despite the generally high yields per step, a major obstacle to the further development of this route was the length of the sequence (11 steps). In addition, there were a number of reactions which might prove to be troublesome upon scaleup. Benzenesulfonation of *ortho*-vanillin (**2**) yielded intermediate **3** which was nitrated with 90% nitric acid to yield a 2:1 mixture of **4a**:**4b**. While recrystallization was very successful in the separation of pure **4a** from the undesired isomer **4b**, one third of the nitration mixture was discarded as the undesired isomer **4b**. Although the hydrolysis of ester **4a** to the sodium or potassium salt **5** was straightforward, the phenoxide proved to be a brightly colored, staining material which caused allergic reactions in some individuals. Alkylation and oxidation converted **5** to nitro acid **7** in good yield. Due to the known explosive nature of *ortho*-nitroaromatic acid chlorides [3], **8** was not isolated but was used in toluene solution to provide diester **9**. Hydrolysis/decarboxylation followed by reduction of the nitro group yielded acetophenone **11**. Treatment of **11** with potassium cyanate in aqueous acetic acid gave **1** as a mixture of monomer and dimer. Treatment with hydrochloric acid smoothly converted the mixture to **12**, the monohydrochloride monohydrate of **1**.

Although other methods of forming the quinazolinone nucleus are known [2,4], the potassium cyanate method utilizing *ortho*-aminoacetophenones was particularly appealing due to the ease with which the reaction is carried out. Isolation of the intermediate urea is generally not necessary and cyclization directly to the quinazolinone occurs in the reaction mixture. With the very favorable cyanate cyclization in mind and with the foreseeable scaleup problems in the original route, it became clear that an improved synthesis of **1** depended on an expedient preparation of 6-amino-2,3-dimethoxyacetophenone (**11**).

The synthesis of aromatic compounds containing four contiguous substituents, as in the case of **11**, has long been a challenge to organic chemists. In classic electrophilic aromatic chemistry, their synthesis has been approached by routes which require the separation of regioisomers as in the original synthesis of **11** or routes which use a blocking group to prevent formation of unwanted isomers and must include steps for introduction/removal of the blocking substituent. More recently this problem has been approached through the use of metalation chemistry, especially where one or more of the desired substituents facilitate metalation [5]. These metalation approaches have often led to significantly shorter

Scheme I

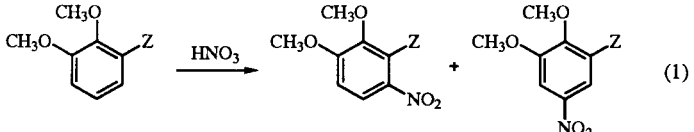


and higher yielding syntheses when compared to classic electrophilic aromatic chemistry.

Results and Discussion.

Nitration Approach.

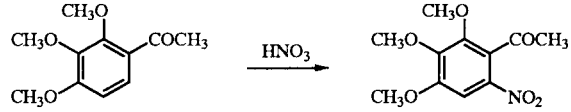
Despite an early literature reference on the lack of selectivity [6], the nitration of 2,3-dimethoxybenzenes was briefly investigated in our laboratories. The 2,3-dimethoxy-substituted aromatics **13a-c**, upon nitration with 70% nitric acid, all yielded an approximately 1:1 ratio of desired isomers **14a-c** to undesired isomers **15a-c** (eq 1).



13a, Z = CHO
13b, Z = $COCH_3$
13c, Z = CO_2H

(1)

Reduction of the nitration mixtures, **14a/15a** and **14b/15b**, gave their corresponding amine isomers which could only be separated chromatographically. The nitro acids **14c/15c**, however, could be separated by *p*H adjustment [7]. Although this procedure was readily performed, a large amount of material was lost thus making it uneconomical for larger scale preparations. Interestingly, nitration of 2,3,4-trimethoxyacetophenone (**16**) cleanly gave a single product, **17** (eq 2) [8].



(2)

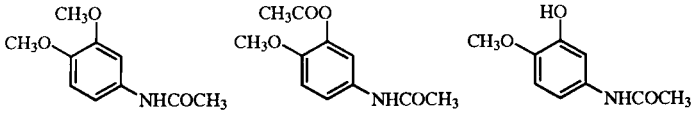
The results obtained in our nitration studies confirmed the literature reports and convinced us to pursue other avenues for the preparation of our key intermediate **11**.

Electrophilic Acylation Approach.

The literature contains a large number of examples of *ortho*-directed acylations such as the Fries rearrangement [9], the photo-Fries [10], and other *ortho*-directed

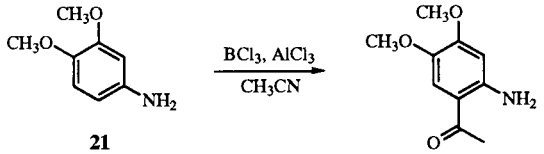
processes [11]. In addition, some examples are available which demonstrate specific *ortho*-substitution of amine compounds [12]. However, our review of the literature also showed that acylations directed between two *meta* substituents were rare and often of low yield. This was especially true if the position *para* to a directing group was open [13]. Nevertheless, we decided to make a brief investigation of this approach.

In our work, we found that acyl migration with the acetamide of 3,4-dimethoxyaniline (**18**) using boron trifluoride etherate or trifluoroacetic acid was not successful. Treatment of **19** with aluminum chloride either neat or in chlorobenzene led mainly to *O*-deacylation and not to desired product. Acylation (aluminum chloride/acetic anhydride) of **20** also gave none of the desired *ortho*-substituted product.



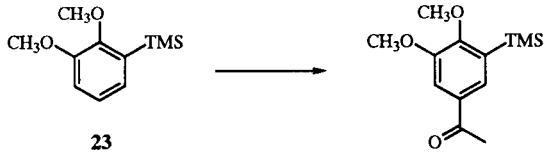
18 **19** **20**

Boron trichloride [12a] catalyzed acylation of **19** gave no product while treatment of 3,4-dimethoxyaniline (**21**) yielded the regioisomeric ketone **22** in trace quantities (eq 3).



21 **22** (3)

One last attempt at acylation included the *ipso* reaction [14] of silane **23** with acetic anhydride which gave mainly the acetylated silane **24** which was partially desilyated under the reaction conditions (eq 4).



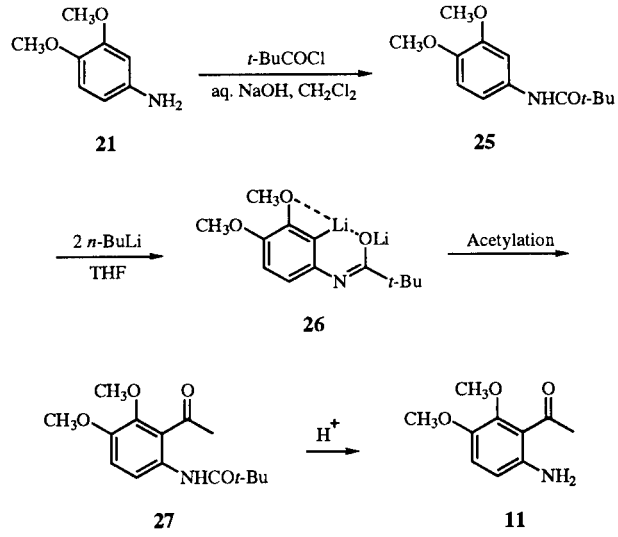
23 **24** (4)

Metalation Approach.

The problems with the electrophilic aromatic chemistry outlined above led us to consider aromatic metalation. This chemistry proved to be a fruitful area of investigation and gave us a practical method for the preparation of our key intermediate **11** on a multi-kilogram scale.

At the inception of our work the literature contained numerous examples of heteroatom directed metalation [15]. Fuhrer and Gschwend had shown that the pivalamide of 3-methoxyaniline could be regioselectively metalated and reacted with a variety of electrophiles [15]. With this literature precedent in hand, we decided to examine the metalation and the subsequent acylation of 3',4'-dimethoxy-2,2-dimethylpropioanilide (**25**). This anilide, which is derived from readily available 3,4-dimethoxyaniline (**21**), has the requisite directing groups for the regioselective metalation [16]. Our initial plan, shown in Scheme II, was to prepare the pivalamide, metalate, acetylate, and then hydrolyze to the key intermediate **11**.

Scheme II



21 **25** **26** **27** **11**

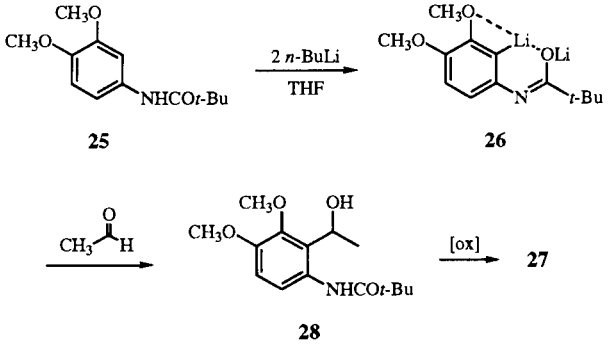
The first task was to show that the metalation of **25** was feasible and that the derived organolithium intermediate was stable for an extended period of time. The stability was a particular concern for larger scale preparations. Pivalamide **25** was conveniently prepared from 3,4-dimethoxyaniline (**21**) and pivaloyl chloride in a two-phase methylene chloride-aqueous sodium hydroxide system. The yields normally ranged from 80-85% but on occasion dropped to as low as 62%. The yield appeared to be highly dependent on the quality of **21** and the higher yields could be consistently obtained by using recrystallized starting material. Metalation of **25** proceeded smoothly in tetrahydrofuran at 0-10° with two equivalents of *n*-butyllithium in hexane. The addition of the second equivalent resulted in the precipitation of the aryllithium intermediate. Quenching of the aryllithium intermediate with deuterium oxide gave complete and regiospecific

deuterium incorporation at the desired position as evidenced by ^{1}H nmr spectral data. Stirring the aryllithium intermediate at 0° for extended periods (2.5 hours) before quenching had no effect on the extent or position of deuterium incorporation.

With the excellent metalation results in hand, we began our studies on the acetylation of the organolithium intermediate **26**. A variety of acetylating reagents were used and these included: acetic anhydride, acetyl bromide, acetyl chloride, acetyl fluoride, *N*-acetylimidazole, lithium acetate, acetonitrile, *N*-methoxy-*N*-methylacetamide, dimethylacetamide and trimethyl orthoacetate. Only acetyl fluoride produced a trace (*ca.* 5%) of the desired ketone in these reactions. Evidently, the organolithium intermediate functions as a hindered base and abstracts a proton from the enolizable acylating reagents rather than acting as a nucleophile and attacking the carbonyl carbon of these reagents. A number of modifications were made in an attempt to improve the desired nucleophilic addition. These modifications included changing the temperature of addition, transmetalation (Zn, Zn/Pd, Mn, Mg, Cu, Ce), inverse addition, and addition of diethyl ether or toluene as a cosolvent. Only with the organocopper reagent and acetyl chloride did we see a positive result (35% desired ketone/65% proton quenched by ^{1}H nmr). Realizing the inherent basic character of the organometallic reagents, we abandoned the direct acetylation approach.

We next considered acetaldehyde as a reagent. Acetaldehyde combined high reactivity with a smaller steric bulk and we hoped that this might prove to be a successful alternative to the direct acetylation. An extra step, oxidation of the resultant alcohol, would be required but the proposed process (Scheme III) would still be considerably shorter than the original route (Scheme I).

Scheme III



25 **26** **27** **28**

Initially the results with acetaldehyde at -15-0° were not practical since a 1:1 ratio (^{1}H nmr) of desired alcohol to starting material (proton quench) was found (Table I). However, lowering the temperature to -70° improved the ratio to 9:1 and pure material could be isolated from the mixture by recrystallization. As with the acylating agents, changes to the reaction conditions to improve the reaction and to allow it to be carried out at a higher temperature were not successful. Transmetalation (Mg, Mn, Zn, Cu) was not successful in changing the ratio at higher temperatures.

Table I

Temperature Study of Reaction of Organolithium **26** with Acetaldehyde

Entry	Reaction Temperature, °C	Ratio **28/25** [a]
1	-15 to 0	1/1
2	-30 to -25	3/2
3	-40 to -30	7/3
4	-70 to -65	9/1

[a] By ^{1}H nmr.

In contrast to the direct acylation studies, the use of cosolvents to break up a supposedly aggregated organometallic was more successful with the acetaldehyde reactions (Table II). At higher reaction temperatures, the addition of pyridine, benzene, or toluene to the organometallic solution before the addition of acetaldehyde had a positive effect on the ratio of alcohol (addition) to starting material (proton quench). Unfortunately, scaleup of these conditions gave variable results which made the technique unreliable for preparing larger amounts of material.

Table II

Co-solvent-Temperature Study on Reaction of Organolithium **26** with Acetaldehyde

Entry	Co-solvent [a]	T, °C	Ratio **28/25** [b]
1	33% Toluene	-15 to -10	13/7
2	33% Benzene	-15 to -10	4/1
3	7% Pyridine	-15 to -10	7/3
4	20% Pyridine	-15 to -10	17/3
5	8% Toluene	-25 to -20	7/3
6	20% Toluene	-25 to -20	17/3
7	8% Toluene	-40 to -30	17/3

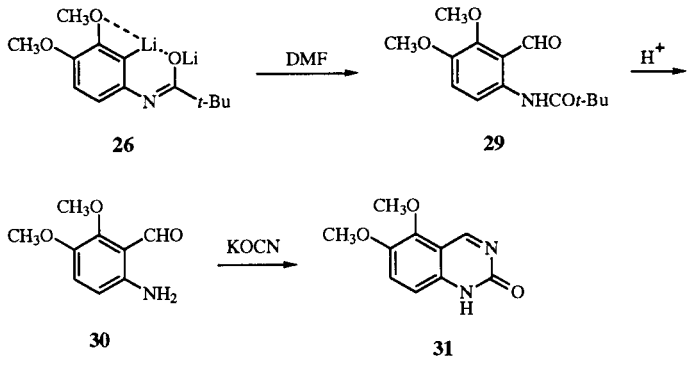
[a] % Co-solvent added compared to amount of tetrahydrofuran. [b] By ^{1}H nmr.

We were able to generate relatively large quantities of alcohol **28** in the laboratory by using the standard -40 to -70° reaction followed by a recrystallization. Unexpectedly our next problem became one of completely oxidizing the alcohol to ketone **27**. Although a large number of oxidation conditions were examined, the best results were obtained with a two-phase dichromate system using a large excess of chromium reagent. With the desired ketone **27** in hand, only a deprotection of the pivalamide to the free amine was needed to yield our key intermedi-

ate **11**. The hydrolysis of **27** with hydrochloric acid was not clean due to partial demethylation of the 2-methoxy group. The addition of a co-solvent (methanol or ethanol) reduced but did not totally eliminate the demethylation problem. The addition of methanol or ethanol substantially increased the reaction time (4 hours to 16 hours) but had the advantage that the pungent pivalic acid by-product was not present in large amounts since the corresponding methyl or ethyl pivalates were produced. Finally to completely avoid the demethylation problem, aqueous sulfuric acid in alcohol was substituted for hydrochloric acid. Although the acetaldehyde route did produce material, the low temperatures required for the acetaldehyde addition coupled with the difficult and messy oxidation made this route unacceptable for the large scale preparation of **11**.

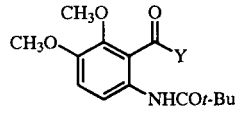
During this time we continued to explore the reaction of the organolithium species **26** with various electrophiles. In contrast to the lack of nucleophilic addition seen with enolizable substrates, the results with non-enolizable compounds or one-carbon reagents were quite encouraging. Addition of dimethylformamide at 0° to the organolithium **26** gave a 77% recrystallized yield of the desired benzaldehyde **29**. Although this material could have been converted to the secondary alcohol **28**, we saw no real advantage since it would still require the tedious oxidation. Instead we had hoped to hydrolyze **29** to the aminoaldehyde **30** and then cyclize to the quinazolinone **31** (Scheme IV). Compound **31** had been converted to our desired final product, 5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone, albeit in low yield [1c]. Unfortunately, we found that **29** could not be deprotected without decomposition, presumably because of the aldehyde and amine functionalities.

Scheme IV



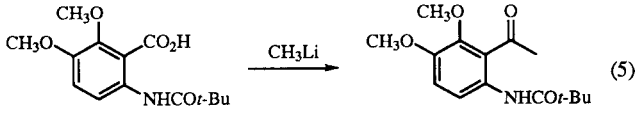
26 **29** **30** **31**

Other non-enolizable reagents included dimethylcarbamyl chloride, trifluoroacetic anhydride, and methyl 4-methoxybenzoate all of which gave quantitative crude yields of the desired products **32**, **33** and **34** upon reaction with **26**.



32, Y = $N(CH_3)_2$
33, Y = CF_3
34, Y = 4-CH_3OPh

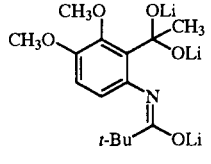
The most useful of the non-enolizable reagents proved to be carbon dioxide. The reaction of carbon dioxide with **26** at 0° gave near quantitative crude yields of the acid **35**. We visualized that we could use this acid for alternative syntheses of our aminoketone **11**. The use of this acid was attractive since the metalation and reaction could be carried out at moderate temperatures and the carboxylic acid functionality provided a handle for simple acid-base purification following the metalation. Initially, we hoped to convert the acid **35** to ketone **27** by reaction with methyllithium (eq 5).



(5)

35 **27**

When acid **35** was treated with methyllithium (3 equivalents) in ether, only traces of the desired ketone **27** could be found by tlc and nmr. The major product of the reaction under a variety of conditions was pivalamide **25**! One interpretation of this result is that the desired addition of methyllithium takes place to form an intermediate trilithio species **37**.

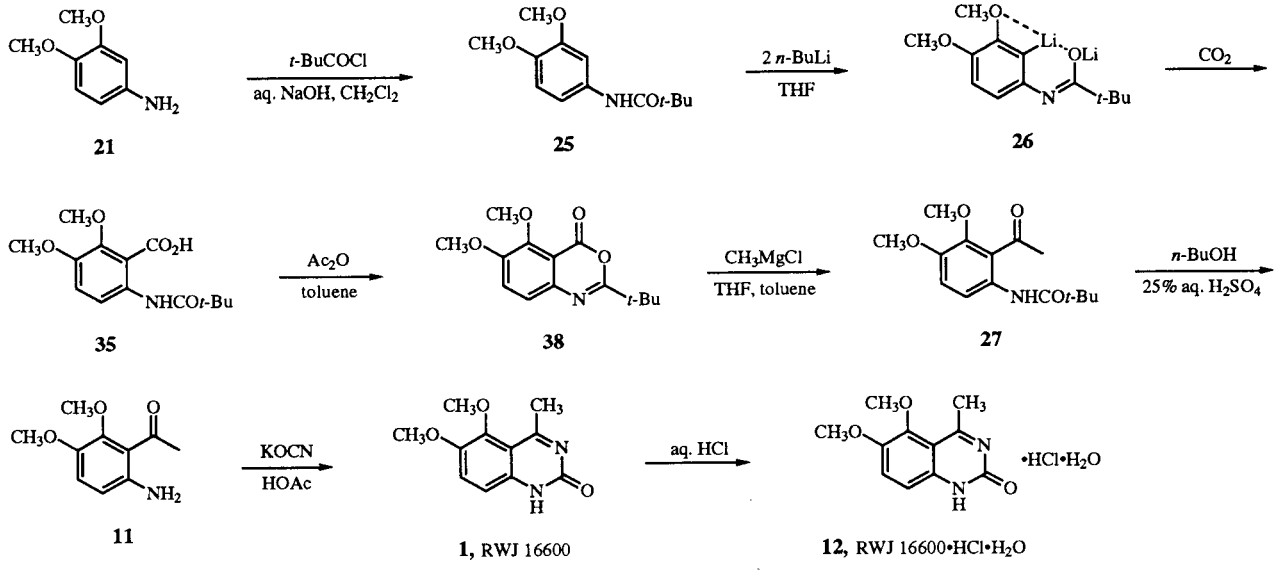


37

This trilithio species decomposes to the *ortho*-lithiated pivalamide **26** and lithium acetate. The *ortho*-lithiated pivalamide **26** was detected upon workup as **25**.

Having failed to produce ketone **27** directly from the acid, we thought the ketone might be available through the benzoxazine **38** (Scheme V). The benzoxazine **38** was readily prepared by cyclization of acid **35** with acetic anhydride in heptane. Reaction of benzoxazine **38** in tetrahydrofuran with methylmagnesium chloride gave the desired ketone **27**. The hydrolysis of **27** to the desired aminoketone **11** was accomplished by refluxing in a 25%

Scheme V



aqueous sulfuric acid/1-butanol solution. The higher boiling 1-butanol helped shorten the hydrolysis time which seemed to lengthen with either methanol or ethanol as the reaction was scaled up. After demonstrating this synthetic approach to the pivotal aminoketone **11**, we decided that the proper choice of conditions in the reaction sequence would enable us to use toluene as the major solvent through the four steps with considerable savings in manipulation of isolated materials and in the use of other solvents. To initiate this plan, the acid **35** was isolated from the lithiation-carbonation reaction by extraction into toluene. The toluene extract containing **35** was then treated with one equivalent of acetic anhydride to give a quantitative (hplc) conversion to the benzoxazine **38**. Reaction of **38** in toluene with methylmagnesium chloride in tetrahydrofuran gave the desired ketone **27** in approximately 85% yield (hplc). The toluene solution of ketone **27** was then prepared for hydrolysis by exchanging the toluene for 1-butanol. Following the hydrolysis, the aminoketone **11** was isolated in a 41% (**25** to **11**) overall yield. Conversion of **11** to **1** was accomplished with potassium cyanate in acetic acid. Treatment of **1** with hydrochloric acid yielded the hydrochloride hydrate **12**.

Summary.

During our investigations into the synthesis of our lead cardiotonic **1**, we explored several alternative synthetic routes. Of these alternative routes, the most useful route proved to be a directed metalation approach starting with the readily available starting material, 3,4-dimethoxyaniline (**21**). Metalation of the pivalamide **25** derived from **21** with *n*-butyllithium was complete and regiospecific for the position flanked by the methoxy and pivalamide directing groups. Because of its hindered nature, the organolithium species **26** appears to function as a base with a variety of enolizable reagents while reacting as a nucleophile with non-enolizable compounds. The most useful of the non-enolizable reagents proved to be carbon dioxide which generated acid **35** from **26**. Compound **35** was converted in good yields to our desired intermediate **11** and ultimately to **1** and its hydrochloride salt **12**. This route (Scheme V) was adaptable to pilot plant scale operations and was used to prepare several kilograms of **12** for clinical trials.

EXPERIMENTAL

Small scale probe metalation reactions were carried out under dry nitrogen in oven-dried apparatus using tetrahydrofuran distilled from a purple solution of sodium benzophenone ketyl. Preparative runs utilized glassware or vessels flushed with dry nitrogen and solvent purchased as the "anhydrous" grade. 3,4-Dimethoxyaniline was purchased from a variety of sources with the bulk supplier being SSF Dottikon. Larger amounts of *n*-butyllithium in hexane or heptane were purchased from Foote Mineral Company. The ^{1}H nmr spectra were recorded at 60 (Varian T-60), 90 (Varian 90), 300 (General Electric QE 300), and 400 MHz (Varian XL-400).

3',4'-Dimethoxy-2,2-dimethylpropioanilide (**25**).

A solution of 24.97 g (0.16 mole) of 3,4-dimethoxyaniline **21** in methylene chloride (50 ml) was added to 2*N* sodium hydroxide (93 ml) and the reaction mixture was cooled to 10°. Pivaloyl chloride (20.2 ml, 0.16 mole) was added over 35 minutes and the reaction mixture was then stirred for 1 hour at room temperature. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 100 ml). The combined methylene chloride layers were dried with magnesium sulfate, Darco treated, and filtered. The resulting methylene chloride

solution was slowly added to heptane (300 ml) which was warmed to 40°. A fluffy solid precipitated during the addition and the mixture was then cooled to 0°. The product was filtered, washed with heptane, and dried under vacuum at 55° to give 38.7 g (90%) of **25**, mp 127.0-127.5°; ir (potassium bromide): 3300, 1650 cm^{-1}; ms: (EI) 238 (M^+); ^1H nmr (deuteriochloroform): δ 1.30 (s, 9H, C-CH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.80 (m, 2H, ArH), 7.27 (br s, 1H, NH), 7.42 (m, 1H, ArH).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.53; H, 8.41; N, 5.77.

Stability of Organolithium **26**.

A solution of **25** (1.18 g, 5 mmoles) in dry tetrahydrofuran (10 ml) was prepared and *n*-butyllithium (10 mmoles, 6.4 ml of 1.57 *M* solution in hexane) was added at <10°. The resulting suspension was stirred at 0° for 2.5 hours before quenching with deuterium oxide (0.5 ml). The reaction mixture was stirred for 30 minutes and then diluted with methylene chloride (50 ml). The organic layer was washed with saturated ammonium chloride (25 ml), separated, and dried (sodium sulfate). Evaporation gave 1.2 g (100%) of **25** which showed nearly 100% of regiospecific deuterium incorporation; ^1H nmr (deuteriochloroform): δ 1.29 (s, 9H, C-CH_3), 3.79 (s, 6H, OCH_3), 6.70 and 6.92 (AB, 2H, ArH), 7.67 (broad s, 1H, NH).

General Procedure for Reaction of Acylation Reagents with Organolithium **26**.

Organolithium **26** was prepared on a 5-20 mmole scale and the resulting suspension cooled to *ca.* -60° before the addition of the acylation reagent. The product was isolated following warming to room temperature and a saturated ammonium chloride workup. The ratio of addition to proton quench was determined by ^1H nmr. For the transmetallations, the metal salt was added at -60° and warmed to 0°. The resultant organometallic was either acylated at 0° or cooled to *ca.* -60° prior to the addition of the acylation reagent.

Reaction of the Organocopper Reagent Derived from **26** with Acetyl Chloride.

A solution of **25** (4.75 g, 20 mmoles) in dry tetrahydrofuran (60 ml) was prepared and *n*-butyllithium (40 mmoles, 26.5 ml of 1.51 *M* solution in hexane) was added at <10°. The resulting suspension was stirred at 0° for 1 hour before the addition of cuprous iodide (3.8 g, 20 mmoles). Addition of cuprous iodide gave a dark brown mixture and a mild exotherm to 10°. Removal of a sample and quenching with deuterium oxide showed nearly quantitative incorporation of deuterium at the desired position. The remaining organocopper reagent was cooled to -50° and acetyl chloride (2.35 g, 30 mmoles) was added. Warming and workup gave material which by ^1H nmr showed a ratio of *ca.* 35% desired ketone **27** to 65% proton quench.

General Procedure for Reaction of Organolithium **26** with Acetaldehyde at Varying Temperatures.

Organolithium **26** was prepared on a 5-20 mmole scale and the resulting suspension was cooled to the various temperatures before the addition of acetaldehyde. The product was isolated following warming to room temperature and a brine workup. The ratio of addition to proton quench was determined by ^1H nmr (Table I):

General Procedure for Reaction of Organolithium **26** with Acetaldehyde in the Presence of a Co-solvent.

Organolithium **26** was prepared on a 5-25 mmole scale and the resulting suspension was cooled to the various temperatures. The dry co-solvent was added before the addition of the acetaldehyde. The product was isolated following warming to room temperature and a brine workup. The ratio of addition to proton quench was determined by ^1H nmr (Table II).

3',4'-Dimethoxy-2'-(α-hydroxyethyl)-2,2-dimethylpropioanilide (**28**).

A solution of **25** (118.5 g, 0.5 mole) in tetrahydrofuran (1.8 l) was prepared and *n*-butyllithium (1.0 mole, 633 ml of 1.58 *M* solution in hexane) was added at <10°. The suspension was stirred at 0° for 1 hour and cooled to -78°. Acetaldehyde (44 g, 1.0 mole) was then added to the organometallic at <-65°. The reaction mixture was warmed to room temperature and diluted with brine (0.5 l). The aqueous layer was separated and extracted with methylene chloride (2 x 250 ml). The combined organic layers were dried (magnesium sulfate), treated with decolorizing carbon, filtered, and evaporated to an oil. The oil was crystallized from 50% ethyl acetate/hexane (500 ml). After cooling at 0° for 2 hours, filtration, washing with 50% ethyl acetate/hexane, and drying gave 82.8 g (60%) of **28** as a white crystalline solid, mp 113-114°; ir (potassium bromide): 3250, 1640 cm^{-1}; ms: (EI) 281 (M^+); ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, C-CH_3), 1.49 (d, 3H, CH_3), 3.3 (d, 1H, OH), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.57 (m, 1H, CH), 7.9 and 6.73 (AB, 2H, ArH), 9.70 (broad s, 1H, NH).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.91; H, 8.37; N, 5.15.

2'-Acetyl-3',4'-dimethoxy-2,2-dimethylpropioanilide (**27**) from Alcohol **28**.

A solution of **28** (80.0 g, 0.28 mole) in methylene chloride (200 ml) was cooled to 0° and 322 ml of chromic acid reagent (prepared by adding 136 g of concentrated sulfuric acid to 100 g of sodium dichromate in 100 ml of water and diluting to 500 ml) was added. After 1 hour at reflux, an additional 322 ml of oxidizing reagent was added and the mixture refluxed for another 1 hour period. The reaction mixture was cooled, diluted with water (500 ml), and extracted with methylene chloride (3 x 1.0 l). The combined organic layers were treated with decolorizing carbon, dried (magnesium sulfate), filtered, and evaporated to give 60.5 g (77%) of **27** as a red oil; ^1H nmr (deuteriochloroform): δ 1.28 (s, 9H, C-CH_3), 2.61 (s, 3H, $COCH_3$), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.02 and 8.07 (AB, 2H, ArH), 9.90 (broad s, 1H, NH).

2'-Formyl-3',4'-dimethoxy-2,2-dimethylpropioanilide (**29**).

Organolithium **26** was prepared from **25** (11.9 g, 50 mmoles) dissolved in tetrahydrofuran (150 ml) and *n*-butyllithium (100 mmoles, 64 ml of 1.57 *M* solution in hexane). The suspension was cooled to -60° and dimethylformamide (4.0 g, 55 mmoles) was added slowly. After warming to room temperature, the reaction was treated with saturated ammonium chloride (50 ml) and methylene chloride (200 ml). The organic layer was separated, dried (sodium sulfate), filtered, and evaporated to yield 14.3 g (>100%) of brown oil. Combining material from another reaction, a total of 19.9 g of oil was dissolved in hot methanol (25 ml). The solution was cooled to room temperature and water (10

ml) was added to crystallize the product. The slurry was cooled at 0° and filtered. The precipitate was washed with cold 5:2 methanol-water and dried to give 15.3 g (77% recovery) of **29** as yellow crystals, mp 62-64°; ir (potassium bromide): 1671, 1661 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.34 (s, 9H, C-CH_3), 3.89 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.20 and 8.47 (AB, 2H, ArH), 10.45 (s, 1H, CHO), 11.43 (broad s, 1H, NH).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.40; H, 7.24; N, 5.25.

3',4'-Dimethoxy-2'-dimethylcarbamyl-2,2-dimethylpropioanilide (**32**).

A solution of **25** (2.37 g, 10 mmoles) in tetrahydrofuran (25 ml) was cooled to 0° and *n*-butyllithium (13.8 ml of 1.59 *M* in hexane, 22 mmoles) was added to form **26**. After stirring the white suspension for one hour at 5-10°, dimethylcarbamyl chloride (1 ml, 11 mmoles) was added. The reaction mixture was allowed to warm to room temperature and then quenched with ice (50 ml) and a saturated sodium chloride (100 ml). The reaction mixture was extracted with ether (100 ml) and the ether extract was then washed with saturated sodium chloride (100 ml). The ether was dried over magnesium sulfate and evaporated to give 3.02 g (98%) of **32** as an oil; ir (neat): 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, C-CH_3), 2.85 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.87 and 7.52 (AB, 2H, ArH), 8.07 (br s, 1H, NH).

3',4'-Dimethoxy-2'-trifluoroacetyl-2,2-dimethylpropioanilide (**33**).

Organolithium **26** was prepared from **25** (11.9 g, 50 mmoles) dissolved in tetrahydrofuran (150 ml) and *n*-butyllithium (100 mmoles, 64 ml of 1.57 *M* solution in hexane). The suspension was cooled to -60° and trifluoroacetic anhydride (11.55 g, 55 mmoles) was added slowly. After the usual ammonium chloride workup, 17.2 g (>100%) of **33** was isolated as a brown oil; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, C-CH_3), 3.86 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.04 and 7.60 (AB, 2H, ArH), 8.5 (broad s, 1H, NH).

3',4'-Dimethoxy-2'-(4-methoxybenzoyl)-2,2-dimethylpropioanilide (**34**).

Organolithium **26** was prepared from **25** (11.9 g, 50 mmoles) dissolved in tetrahydrofuran (150 ml) and *n*-butyllithium (100 mmoles, 64 ml of 1.57 *M* solution in hexane). Methyl 4-methoxybenzoate (8.64 g, 52 mmoles) was added to the suspension at 0°. The reaction mixture was stirred at room temperature for one hour before the usual ammonium chloride workup to yield 21.7 g (>100%) of **34** as a brown oil; ^1H nmr (deuteriochloroform): δ 1.28 (s, 9H, C-CH_3), 3.61 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.8-7.95 (m, 6H, ArH), 8.1 (broad s, 1H, NH).

2'-Carboxy-3',4'-dimethoxy-2,2-dimethylpropioanilide (**35**).

The organolithium **26** was prepared at 0° from **25** (10 g, 42 mmoles) dissolved in tetrahydrofuran (100 ml) and *n*-butyllithium (60 ml, 87 mmoles, 1.45 *M* in hexane). At 0°, carbon dioxide gas (bone dry) was bubbled below the surface for 30 minutes. The reaction mixture was quenched with water (50 ml) and acidified with concentrated hydrochloric acid (15 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 ml). The combined organic layers were washed with 2 *N* sodium hydroxide (100 ml) and the base layer was back extracted with ethyl acetate (50 ml). The base layer was acidified with concentrated hydrochloric acid (15 ml) and then extracted with ethyl acetate (2 x 50 ml). The combined ethyl acetate extracts were dried over magnesium sulfate, Darco treated, and concentrated to a volume of ~10 ml. The concentrate was diluted with *n*-heptane (40 ml) to induce crystallization. Filtration, washing with 5% (v/v) ethyl acetate/heptane, and drying under vacuum at 60° gave 8.73 g (76%) of **35** as cream crystals, mp 94.5-97.0°; ir (potassium bromide): 3322, 1694 cm^{-1}; ms: (EI) 281 (M^+); ^1H nmr (deuteriochloroform): δ 1.33 (s, 9H, C-CH_3), 3.90 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 7.13 and 8.52 (AB, 1H, J = 10 Hz, ArH), 10.87 (br s, 1H, NH or CO_2H), 11.25 (br s, 1H, NH or CO_2H).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.44; H, 7.01; N, 4.88.

2-(1,1-Dimethylethyl)-5,6-dimethoxy-4*H*-3,1-benzoxazin-4-one (**38**).

A solution of **35** (20 g, 70 mmoles), acetic anhydride (10 ml, 105 mmoles), and heptane (100 ml) was refluxed for one hour. The reaction mixture was rotary evaporated to a thick brownish oil and dissolved in ether (300 ml). The ether solution was extracted with 1% sodium bicarbonate (200 ml), dried over magnesium sulfate and then rotary evaporated to 18.1 g of crude white solid. The crude material was dissolved by heating in heptane (100 ml) and allowed to crystallize by cooling to room temperature. After cooling at 0° for 1 hour, the material was filtered, washed with cold heptane (30 ml), and dried under vacuum at 45° to give 16.25 g (88%) of **38** as a white fluffy solid, mp 79.0-79.5°; ir (potassium bromide): 1758 cm^{-1}; ms: (CI) 264 (MH^+); ^1H nmr (deuteriochloroform): δ 1.35 (s, 9H, C-CH_3), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.30 (s, 2H, ArH).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.98; H, 6.63; N, 5.40.

2'-Acetyl-3',4'-dimethoxy-2,2-dimethylpropioanilide (**27**) from Benzoxazinone **38**.

A solution of **38** (12.4 g, 47 mmoles) in tetrahydrofuran (50 ml) was prepared and cooled to 0°. A solution of methylmagnesium chloride in ether (3.2 *M*, 36.7 ml, 118 mmoles) was added slowly while keeping the temperature between 15-25°. Stirring was continued at 0° for 30 minutes and then saturated ammonium chloride (10 ml) was cautiously added. Additional saturated ammonium chloride (90 ml) was added and the reaction mixture was extracted with ether (3 x 100 ml). The combined ether extracts were washed with saturated sodium carbonate (2 x 50 ml) and dried over sodium sulfate. Rotary evaporation gave 12.4 g (94%) of **27** as an oil which slowly solidified on standing: ir (neat): 3350, 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (s, 9H, C-CH_3), 2.63 (s, 3H, $COCH_3$), 3.88 (s, 6H, OCH_3), 7.02 and 8.07 (AB, 2H, J = 9 Hz, ArH), 9.88 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.02. Found: C, 64.24; H, 8.08; N, 4.97.

2'-Acetyl-3',4'-dimethoxy-2,2-dimethylpropioanilide (**27**) from 6-Amino-2,3-dimethoxyacetophenone (**11**).

A solution of **11** (1.95 g, 10 mmoles) in methylene chloride (25 ml) was prepared and saturated sodium carbonate (25 ml) was added. A solution of pivaloyl chloride (1.20 g, 10 mmoles) in methylene chloride (5 ml) was then added over one minute. Methylene chloride (25 ml) and water (25 ml) were then added to the reaction mixture. The layers were separated, and the aqueous

layer was extracted with 25 ml of methylene chloride. The combined methylene chloride layers were washed with 25 ml of water and then dried over sodium sulfate. Rotary evaporation gave 2.67 g (96%) of **27** as a yellow-orange oil; ir (neat) and ^{1}H nmr (deuteriochloroform) identical to previously isolated material.

6-Amino-2,3-dimethoxyacetophenone (**11**).

A solution of **27** (25.0 g, 90 mmoles) in 1-butanol (100 ml) and 25% (v/v) sulfuric acid (125 ml) was refluxed for 7.5 hours. The reaction mixture was cooled and diluted with cold water (200 ml). The layers were separated at room temperature and the 1-butanol layer was extracted with 1 *N* hydrochloric acid (2 x 250 ml). The combined aqueous layers were basified with concentrated ammonium hydroxide (250 ml) to *p*H 10 while keeping the temperature at less than 35°. The base solution was then extracted with methylene chloride (2 x 500 ml), dried over magnesium sulfate, Darco treated, and rotary evaporated at less than 50° (**Caution:** product codistills under high vacuum and higher temperatures). The red solution (~54 g) was diluted with heptane (250 ml), seeded, and stirred at 0° for 1 hour. The crystallized product was filtered, washed with heptane (100 ml), and dried under vacuum at room temperature to give 10.6 g (61%) of **11**; mp 60.0-61.0°; ir (potassium bromide): 3475, 3375, 1665 cm^{-1}; ms: (Cl) 196 (MH^+); ^{1}H nmr (deuteriochloroform): δ 2.60 (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.00 (s, 2H, NH_2), 6.33 and 6.90 (AB, 2H, ArH).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.72; N, 7.17. Found: C, 61.34; H, 6.72; N, 7.09.

6-Amino-2,3-dimethoxyacetophenone (**11**) from 3',4'-Dimethoxy-2,2-dimethylpropioanilide (**25**) without Isolation of Intermediates.

Under nitrogen, a solution of **25** (480 g, 2.02 moles) in tetrahydrofuran (4.8 l) was prepared and cooled to 0°. Keeping the reaction below 15°, *n*-butyllithium (1.46 *M* in hexane, 2784 ml, 4.06 moles) was added. The reaction mixture was stirred for one hour at 0-5° and carbon dioxide gas was then bubbled below the surface for 45 minutes. After stirring an additional 45 minutes, 25% (v/v) sulfuric acid (216 ml) was added slowly (effervescence!). The precipitate was filtered, washed with tetrahydrofuran (500 ml), and dried on the filter for 3 hours. The solids were then dissolved in water (4.8 l) and the turbid solution (*p*H = 10) was filtered through Hyflo (100 g). The filtrate was then extracted with methylene chloride (2 x 2.0 l). The aqueous layer was acidified to *p*H 2 with concentrated hydrochloric acid (195 ml) and extracted with toluene (3.0 l). The toluene layer was then treated with Darco (48 g) and filtered through Hyflo (145 g). The Hyflo cake was washed with toluene (1.0 l) and the toluene solution distilled until a vapor temperature of 110° was reached. The final volume was 3.1 l and contained 409 g (1.45 moles/72%) of **35** (hplc: Waters C_{18}•μBondapak, 70:30 methanol-water, 2 ml/minute, uv @ 254 nm). Toluene (2.0 l) and acetic anhydride (1446 ml, 1.52 moles) was added to the above toluene solution of **35**. The solution was heated to reflux and the toluene-acetic acid azeotrope (2.9 l) was collected until the hplc revealed complete conversion to **38**. The toluene solution of **38** was cooled to 0-5° and methylmagnesium chloride (3 *M*, 969 ml, 2.90 moles) in tetrahydrofuran was added (gas evolution) over 30 minutes while keeping the temperature below 30°. The reaction mixture was cooled to 10° and quenched with saturated ammonium chloride (4.8 l). The layers were separated and the aqueous layer was extracted with toluene (3.0 l). The combined toluene solutions were concentrated (4.3 l of distillate collected) to 1 l and methanol (7 l) was added. The solution was heated to reflux and the toluene-methanol azeotrope (5.0 l) was collected. The solution contained 345 g (86%) of **27** (hplc). To the methanol solution (2 l) containing **27** (345 g, 1.24 moles) was added 25% (v/v) sulfuric acid (3.6 l). The reaction mixture was heated at reflux (86°) for 30 hours, cooled to 40°, and diluted with cold water (5°, 2.0 l). The reaction mixture was extracted with methylene chloride (2 x 2.0 l). The aqueous layer was cooled, basified with concentrated ammonium hydroxide (1.3 l) to *p*H 10, and extracted with methylene chloride (3 x 2.5 l). The combined methylene chloride extracts were dried over magnesium sulfate (300 g), treated with Darco (40 g), and filtered through Hyflo (145 g). The filter cake was washed with methylene chloride (500 ml) and the filtrate evaporated to a crude oil (215 g). The crude oil was dissolved in 2-propanol (120 ml) and heptane (1180 ml) was added. After cooling at 0° for 3 hours, the product crystallized. The material was filtered, washed with heptane (500 ml), and dried under vacuum at 30°. **11** (161 g, 66%, 41% overall yield from **25**) was obtained as yellow crystals, mp 59.0-61.0°.

5,6-Dimethoxy-4-methyl-2(1*H*)-quinazolinone Hydrochloride Hydrate (**12**).

A solution of **11** (150 g, 0.77 mole) in acetic acid (600 ml) was prepared and cooled to 15°. A filtered solution of potassium cyanate (75 g, 0.91 mole) in water (300 ml) was added slowly while keeping the temperature below 35°. The reaction mixture was stirred at room temperature for 2 hours and then cooled at 0° for 2 hours. The product was filtered, washed with cold water (250 ml), washed with cold acetone (2 x 250 ml), and dried under vacuum to give 155 g (91%) of the free base **1** as yellow crystals, mp 237-240°. The free base (155 g, 0.70 mole) was dissolved in concentrated hydrochloric acid (1875 ml) which had been cooled to 15°. Additional concentrated hydrochloric acid (375 ml rinse) was added and the red solution was cooled to 10°. Water (2250 ml) was then added while keeping the temperature below 35°. The reaction mixture was cooled at 5-10° for 2 hours, filtered, washed with cold acetone (750 ml), dried on the filter for 2 hours, and then dried under vacuum at 60° to give 176 g (92%) of **12** as yellow-orange crystals, mp 215.0-217.0°.

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